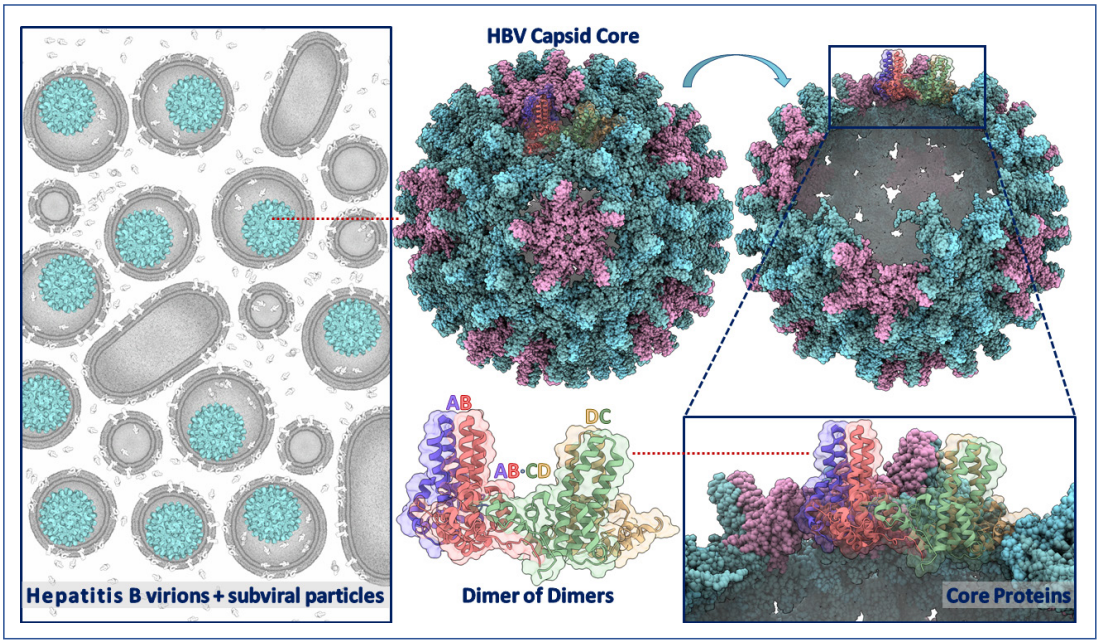
Print ISSN: 2434-9186 Online ISSN: 2434-9194

NCGM

Global Health & Medicine

Volume 5, Number 4
August, 2023



Structure of the hepatitis B virus (HBV) capsid core (Page 200)

www.globalhealthmedicine.com

Print ISSN: 2434-9186
Online ISSN: 2434-9194
Issues/Year: 6
Language: English

NCGM

GHM
Global Health & Medicine

Global Health & Medicine

Global Health & Medicine (Print ISSN 2434-9186, Online ISSN 2434-9194) is an international, open-access, peer-reviewed journal, published by the National Center for Global Health and Medicine (NCGM), which is a national research and development agency in Japan that covers advanced general medicine, basic science, clinical science, and international medical collaboration.

1. Mission and Scope

Global Health & Medicine is dedicated to publishing high-quality original research that contributes to advancing global health and medicine, with the goal of creating a global information network for global health, basic science as well as clinical science oriented for clinical application.

The articles cover the fields of global health, public health, and health care delivery as well as the seminal and latest research on the intersection of biomedical science and clinical practice in order to encourage cooperation and exchange among scientists and healthcare professionals in the world.

2. Manuscript Types

Global Health & Medicine publishes Original Articles, Brief Reports, Reviews, Policy Forum articles, Communications, Editorials, Letters, and News on all aspects of the field of global health and medicine.

3. Editorial Policies

Global Health & Medicine will perform an especially prompt review to encourage submissions of innovative work. All original research manuscripts are to be subjected to an expeditious but rigorous standard of peer review, and are to be edited by experienced copy editors to the highest standards.

We aspire to identify, attract, and publish original research that supports advances of knowledge in critical areas of global health and medicine.

Print ISSN: 2434-9186
Online ISSN: 2434-9194
Issues/Year: 6
Language: English

NCGM

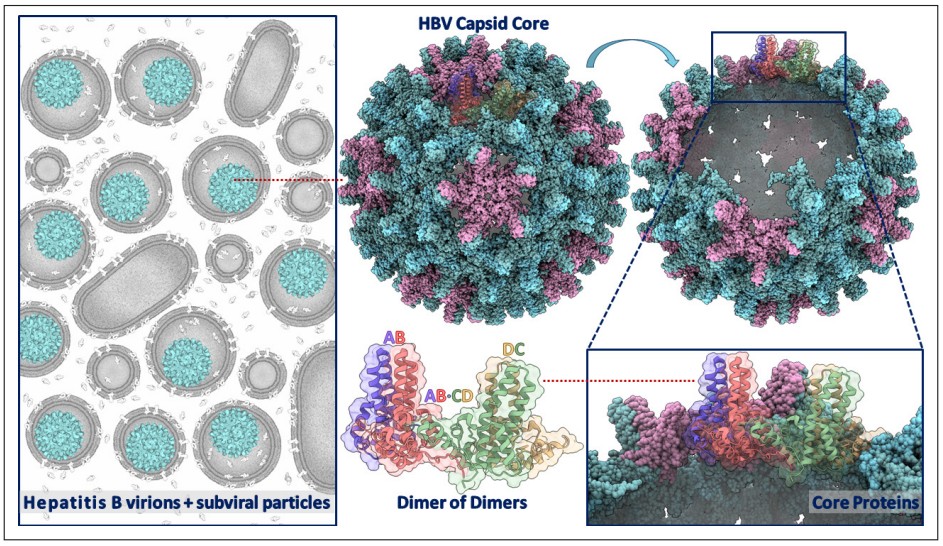
Global Health & Medicine

CONTENTS

Volume 5, Number 4, 2023

CONTENTS (Continued)

COVER FIGURE OF THIS ISSUE



Structure of the hepatitis B virus (HBV) capsid core. [Left] Rendition of released particles from HBV infection, including mature virions with assembled capsids (PDB: 6HTX) and core protein (Cp) dimers (PDB: 6ECS) as well as both non-infectious subviral particles and excreted HBV E Antigen (HBeAg, PDB: 3V6Z). No full structure of HBV Surface Antigen (HBsAg) is deposited in the PDB; partial HBsAg (PDB: 7TUK) and CD9 (PDB: 6K4J) protein embedded in the default membrane structure from cellPAINT to represent the viral envelope (in grey). The mature capsid shown in blue and all other proteins in white. The P•pgRNA complex or P•rcDNA would be located inside the core. Made with cellPAINT (v2.0). [Right] Two orientations of the HBV Capsid core (PDB: 6HTX) with hexamers in cyan and pentamers in pink. One dimer of Cp dimers has the secondary structure shown with distinct colors in each Cp monomer to display protein·protein interactions. Made with ChimeraX (v1.5). (Page 200)

Global Health & Medicine. 2023; 5(4):194-198.
EDITORIAL
DOI: 10.35772/ghm.2023.01013

Four decades of continuing innovations in the development of antiretroviral therapy for HIV/AIDS: Progress to date and future challenges

Arun K. Ghosh[1,2,*]

[1] Department of Chemistry, Purdue University, West Lafayette, IN, USA;
[2] Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, West Lafayette, IN, USA.

Abstract: The treatment of HIV-1 infection and AIDS represents one of the greatest challenges in medicine. While there is no cure for HIV/AIDS, truly remarkable progress has been made for treatment of HIV/AIDS patients today. The advent of combination antiretroviral therapy (cART) in the mid-1990s dramatically improved HIV-1 related morbidity, greatly prolonged life expectancy, and delayed progression of AIDS. Due to current antiretroviral therapy, the mortality rate for HIV infected patients is closely approaching the mortality rate for the general population. The long-term success of HIV-AIDS treatment requires continued enhancement of cART with further development of novel drugs that would exhibit fewer side effects, higher genetic barrier to the development of resistance, and longer action with durable virologic suppression. This editorial article provides a quick review of four decades of intense drug development research efforts targeting various viral enzymes and cellular host factors leading to the evolution of today's treatment of patients with HIV-1 infection and AIDS. It also touches on challenges of future treatment options.

***Keywords*:** AIDS, antiretroviral, HIV, therapy, drug development

It has been four decades now, since the human immunodeficiency virus (HIV), the etiological agent for acquired immunodeficiency syndrome (AIDS), was identified. The first reported case was recorded in 1981. According to the UNAIDS/WHO's report on HIV/AIDS, to date, an estimated 38.4 million patients worldwide have been living with HIV-1 infection and AIDS. Also, an estimated 40.1 million people lost their lives due to HIV and AIDS-related illness since the beginning of the epidemic (*1*). These figures are quite staggering by any measure. Since the early years of the HIV/AIDS epidemic, there has been an unprecedented effort among scientific communities around the world to control the virus with particular emphasis on translation of basic science into the development of antiretroviral therapeutics. This has resulted in intense collaboration between research communities in academic and pharmaceutical laboratories, doctors and health care providers, public health officials, funding agencies, and HIV/AIDS patients. It is a truly remarkable alliance in the history of medicine. The development of novel therapeutic agents and implementation of drug combinations targeting various steps of the HIV life cycle has transformed HIV infection and AIDS from an irrefutably fatal disease into a manageable chronic ailment. However, there is no cure for HIV infection or AIDS yet. The introduction of antiretroviral therapy (ART) dramatically suppressed HIV replication in most patients with HIV infection and AIDS who receive an ART treatment regimen. The clinical outcome then resulted in a significant decline of HIV/AIDS-related mortality, particularly in developed countries where patients have access to potent antiretroviral drug combinations (*2*). The progression and continuous development of new and more effective antiretroviral therapies for the treatment of HIV/AIDS is also an inspiring testament in modern medicine where synthetic organic and innovative medicinal chemistry played a very critical role in the design, development, and evolution of innovative antiretroviral drugs.

In early days of the 1980s, HIV/AIDS patients had a life expectancy of about one year, following the diagnosis. The first drug treatment for HIV/AIDS patients began in 1987 when a failed anticancer drug from the 1960s, azidothymidine (AZT), also referred as zidovudine (ZDV, Figure 1), was shown to potently inhibit a viral enzyme reverse transcriptase (RT) (*3,4*). RT catalyzes the transcription of double stranded viral RNA into DNA, an essential step in the viral replication process. This nucleoside reverse transcriptase

inhibitor (NRTI) gets phosphorylated *in vivo* and blocks enzymatic function of RT by incorporating the nucleotide analog and causing chain termination. AZT suppressed HIV replication, reduced opportunistic infection, and extended lives of HIV/AIDS patients. AZT marked the first drug treatment for HIV/AIDS patients. Other NRTI such as, didanosine (ddI) and dideoxycytidine (ddC) were subsequently approved in the early 1990's. These RT inhibitor drugs proved useful however, toxicity and resistance development compromised their effectiveness (*5*). The approval of AZT and other NRTIs paved the way for development of several new classes of antiretroviral therapies targeting other critical viral targets. Also, development of several effective HIV diagnostic tests, particularly those measuring viral loads and CD4+ cell counts further accelerated the drug development process.

The breakthrough in the development of novel antiretroviral therapeutics targeting other biochemical mechanisms occurred in the mid-1990s. The approval of HIV-1 protease inhibitor drugs marked the beginning of a new era of HIV/AIDS treatment. Protease inhibitor research efforts also became a hallmark of innovation in modern drug discovery and medicinal chemistry. Early knowledge of virus replication established that HIV-1 protease plays a critical role in processing the *gag* and *gag-pol* gene product into essential viral proteins including protease, reverse transcriptase, integrase, and other important structural proteins. Not surprisingly, HIV protease was recognized as an important biochemical target for drug development, early on. Consequently, a significant effort towards design, discovery, and development of HIV-1 protease inhibitor drugs then intensely followed in both academic and pharmaceutical laboratories. The HIV-1 protease is an aspartic acid protease. It is a homodimeric enzyme with two 99-amino acid subunits with each monomer contributing a catalytic aspartic acid functional group to form the active site. The human genome features several other aspartic acid proteases that play critical roles in the pathogenesis of human diseases. Previous drug discovery efforts against these aspartic acid proteases included renin inhibitor design for treatment of hypertension. Early work on renin inhibitors did not translate into any approved drugs however, it provided important groundwork in terms of mechanism-based design for HIV-1 protease inhibitors. The challenging goals of HIV-1 protease inhibitor design were to develop selective, metabolically stable, and orally bioavailable inhibitor drugs. A massive research effort in academic and pharmaceutical laboratories began with the goal of developing HIV-1 protease inhibitor drugs.

The first HIV-1 protease inhibitor drug, saquinavir (SQV, Figure 2) received FDA approval in the mid-

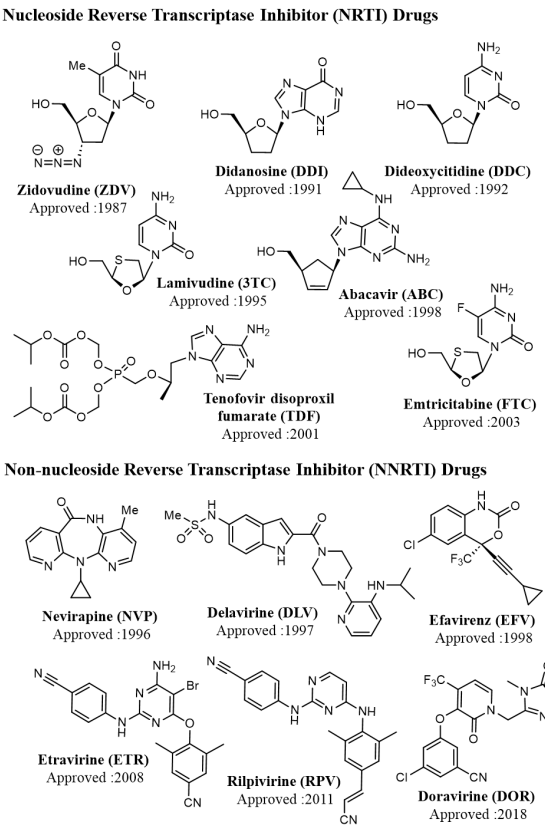


Figure 1. Structures of approved RT inhibitor drugs.

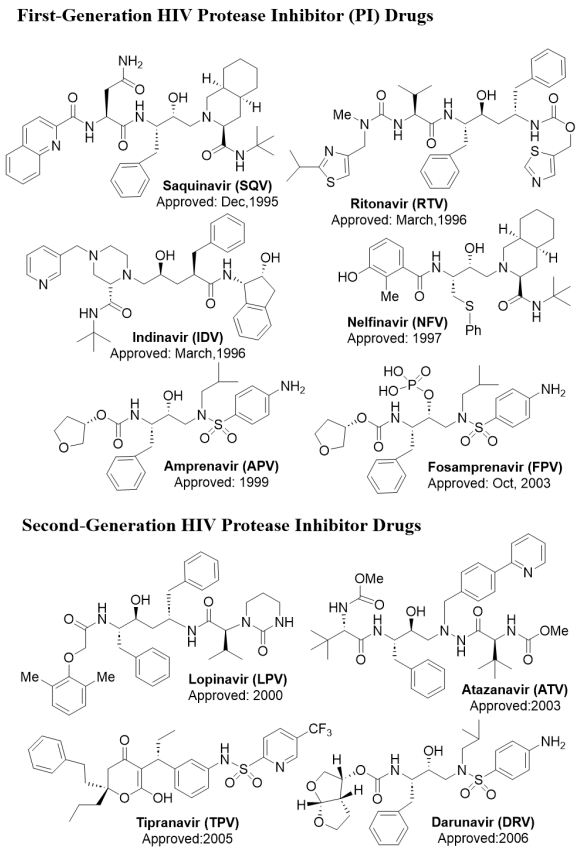


Figure 2. Structures of approved HIV-1 protease inhibitor drugs.

1990s (*6,7*). Subsequently, other protease inhibitor drugs, such as ritonavir followed by indinavir, and nelfinavir were approved by the FDA. These protease inhibitors were then incorporated into highly active antiretroviral therapy (HAART) with reverse transcriptase inhibitor drugs developed earlier. The HAART treatment regimens have had dramatic impact on management of HIV-1 infection and suppression of HIV-1 replication in treated patients. This led to a significant improvement in life expectancy and mortality rates of HIV/AIDS patients who have access to these therapies in developed countries. The HAART treatment regimens immensely improved the prognosis of the AIDS epidemic by transforming HIV/AIDS into a manageable chronic disease (*8,9*). Despite this major progress, early PI-based therapies were often rendered ineffective due to emergence of drug-resistant HIV-1 variants. Therefore, a second generation of nonpeptide protease inhibitor drugs such as atazanavir, lopinavir, tipranavir and darunavir was developed to address these issues. The last approved protease inhibitor drug darunavir (2006) is a widely used PI-drug. Darunavir, is highly potent and has been shown to be particularly effective in treatment of patients harboring drug-resistant HIV-1 variants (*10,11*).

In the mid-1990s another class of antiretroviral drugs, called non-nucleoside reverse transcriptase inhibitor (NNRTI) was developed (*12,13*). Unlike NRTIs, NNRTIs do not require *in vivo* phosphorylation to exert their inhibitory activity. This drug class includes nevirapine and efavirenz. They block HIV replication by noncompetitive inhibition of RT and bind to a hydrophobic pocket in the subdomain of p66, located 10Å away from the active site of RT, known as the NNRTI pocket. Subsequently, other NNRTI drugs such as etravirine, rilpivirine, emtricitabine and doravirine were developed. These drugs along with a newer class of NRTIs such as abacavir, tenofovir, lamivudine and emtricitabine were effectively utilized in various combination therapies to control HIV-1 infection and AIDS.

Drug discovery efforts targeting viral entry led to the development of a new class of drugs. As mentioned earlier, HIV-1 replication is a multistage process where viral attachment and viral fusion are critical early stages of the replication cycle. Viral attachment involves interaction of the viral gp120 protein with the CD4 protein on the surface of the T-cell. HIV enters the T-cell by a fusion process, which is facilitated by the viral protein gp41 and the CCR5 and CXCR4 coreceptors on the T-cell. Both the viral entry and viral fusion have been targeted to block the viral replication cycle. The first entry inhibitor enfuvirtide received FDA approval in 2003. Enfuvirtide (T-20, Figure 3) is a 36 amino-acid synthetic peptide (*14*). It mimics amino acids 127–162 which is located in heptad repeat-2 (HR-2) in the HIV gp41 envelope glycoprotein subunit. Its mechanism of action involves binding to the residues in HR-1 and blocking a conformational change in gp41 necessary for fusion of the lipid envelope of HIV with the membrane of CD4 T cells, thus preventing viral entry. It was developed to target gp41 protein as an injectable drug. The second entry inhibitor is maraviroc approved in 2007 (*15*). This drug blocks the interaction of HIV-1 gp120 protein with the CCR5 coreceptor on the target cell. Maraviroc is used in combination with other anti-HIV drugs. HIV-1 can use other coreceptors for viral entry and maraviroc may not be effective for all patients. Therefore, an HIV-1 tropism test is necessary to determine if the drug would be useful for a particular patient group.

The latest class of approved anti-HIV drugs is Integrase strand transfer inhibitors (INSTIs) (*16,17*). The first orally active integrase inhibitor drug raltegravir (Figure 3) was approved in 2007. HIV-1 integrase is a key enzyme involved in integration of proviral DNA created by reverse transcriptase into host T-cell DNA by formation of a covalent bond between viral DNA and host T-cell DNA. In essence, blocking of integrase enzyme function would prevent incorporation of viral DNA into host cell DNA, an essential step for viral replication. Inhibition of this vital step has also been recognized as a critical target for drug development. Since approval of the first INSTI drug raltegravir in 2007, other INSTIs such as elvitegravir in 2012, dolutegravir in 2013, and cabotegravir in 2021 were approved for treatment of HIV/AIDS patients. Introduction of the antiretroviral agents in cART led to excellent suppression of HIV-1 replication in the vast

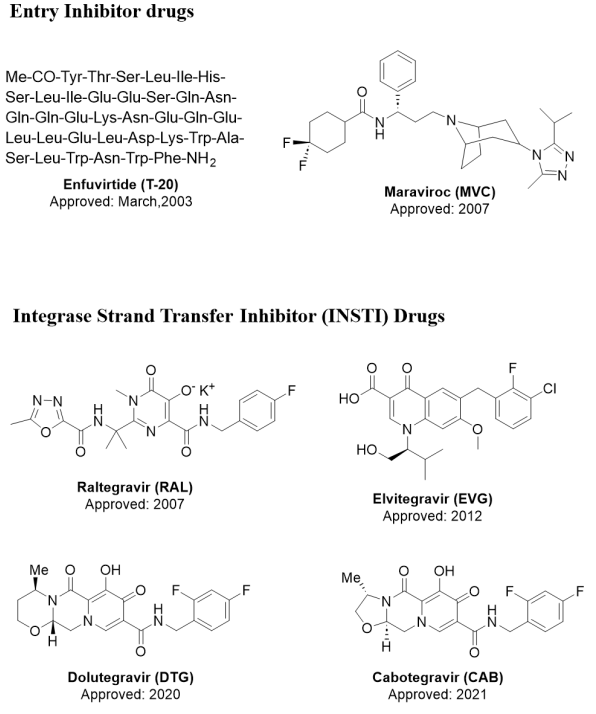


Figure 3. Structures of approved entry inhibitor and integrase inhibitor drugs.

majority of HIV/AIDS patients.

To date, more than 30 anti-HIV drugs targeting many different viral replication mechanisms have been approved (*18*). These drugs provide many choices to individualize drug treatment. Due to issues related to safety, tolerability, pill burden, and dosing frequency, not all approved drugs are used clinically. Current less toxic and more efficacious treatment regimens evolved from the earlier grueling experience of large pill burden, drug toxicities, drug-drug and food-drug interactions, inadequate viral suppression, and emergence of drug-resistant variants. Today, multidrug combinations are the key to suppress viremia and delay emergence of drug resistance. cART needs to continue indefinitely as even a temporary halt in cART results in rapid viral rebound in almost all patients due to the persistence of viral reservoirs in HIV infected patients. The use of older NRTIs is limited due to severe mitochondrial, bone marrow toxicities, and peripheral neuropathy (*19*). The first-generation protease inhibitors drugs paved the way for cART treatment regimens with RT inhibitor drugs, which changed the course of the HIV epidemic dramatically. However, their use has been limited due to poor drug properties, ranging from peptide-like features, low oral bioavailability, metabolic instability, PI-associated lipodystrophy, and other side effects. More potent and less toxic, second-generation PI-drugs are mostly used clinically. Interestingly, the first-generation PI drug, ritonavir however is used in low doses with other PI drugs as a pharmacokinetic booster. Low doses of ritonavir are ineffective against HIV, but they inhibit the CYP-3A4 metabolizing enzyme, improves oral bioavailability and duration of action of other PI drugs. The viral entry inhibitor, enfuvirtide is a large synthetic peptide with a short plasma half-life. While it is an effective antiretroviral agent, its clinical use is limited as the drug needs to be injected subcutaneously, twice daily and often results in side effects at the injection sites. The other entry inhibitor maraviroc is a CCR5 antagonist which is approved for both treatment of naïve and treatment experienced patients by blocking R5-tropic HIV entry into CD4 cells. However, its clinical use is limited as the drug requires inconvenient tropism testing and needs twice daily dosing (*20*).

The development of drug resistance represents one of the major causes of HIV treatment failure. At present, boosted second generation protease inhibitors and integrase inhibitor drugs have shown efficacy leading to sustained viral suppression and improved clinical benefits. Among protease inhibitors, boosted darunavir has been shown to be particularly effective. It has shown higher genetic barriers for resistance development compared to other available agents. Darunavir was developed through structure-based design efforts by promoting extensive hydrogen bonding interactions with the highly conserved active site protease backbone atoms. This 'backbone binding concept' turned out to be an effective strategy for combating drug-resistant HIV variants (*21*). Since entry inhibitor drugs interfere with an earlier viral replication step of infection compared to cART, the development of cross-resistance to cART agents is not expected. Both viral entry inhibitor drugs, enfuvirtide and maraviroc are approved for treatment of multidrug resistant HIV strains but their use has been limited. Currently approved integrase inhibitor drugs are effective anti-HIV agents in cART treatment regimens. Among these, dolutegravir has shown a high genetic barrier for resistance development compared to other INSTs, raltegravir and elvitegravir (*22*).

The past four decades of HIV-AIDS drug development efforts targeting various viral enzymes and cellular host factors involved in the HIV-1 replication cycle, led to significant advances in today's HIV-AIDS treatment. While there is no cure for HIV/AIDS, the combination antiretroviral therapy (cART) significantly improved HIV-1 related morbidity, greatly prolonged life expectancy, and delayed or prevented progression of AIDS. In the absence of a cure, the long-term success of HIV-AIDS treatment will require continuation of cART with durable virologic suppression without the emergence of drug-resistant variants. Therefore, current, and future priorities remain to develop more efficacious drugs and develop new drugs targeting novel viral mechanisms to further improve cART regimens with reduced toxicities, improved tolerability, decreased pill burden and extended duration of action. Also, it is critically important to develop innovative therapies that not only improve efficacy and safety over the existing drugs but also delay or prevent the development of drug-resistant HIV-1 variants. Despite much improvement in cART regimens in recent years, HIV-associated neurocognitive disorders, dementia-like symptoms, are increasing at an alarming rate due to viral reservoirs in the CNS and brain. New drug development needs to target persistent HIV reservoirs in the CNS, peripheral blood, and lymphoid tissues. While complete eradication of HIV and a cure appears to be a formidable challenge, the development of more effective cART regimens addressing these issues with the goal of eradication of viral reservoirs, forms an important step forward.

Funding: This research work was supported by funding from the National Institutes of Health (Grant AI150466) and Purdue University.

Conflict of Interest: The author has no conflicts of interest to disclose.

References

1. UNAIDS. Full report — In Danger: UNAIDS Global AIDS Update 2022. *https://www.unaids.org/en/resources/*

documents/2022/in-danger-global-aids-update (accessed February 26, 2023).
2. Braitstein P, Brinkhof MW, Dabis F, *et al.* Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet. 2006; 367:817-824.
3. Mitsuya H, Weinhold KJ, Furman PA, St Clair MH, Lehrman SN, Gallo RC, Bolognesi D, Barry DW, Broder S. 3'-Azido-3'-deoxythymidine (BW A509U): an antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus *in vitro*. Proc Natl Acad Sci U S A. 1985; 82:7096-7100.
4. Fischl MA, Richman DD, Grieco MH, *et al.* The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. N Engl J Med. 1987; 317:185-191.
5. Mitsuya H, Yarchoan R, Broder S. Molecular targets for AIDS therapy. Science. 1990; 249:1533-1544.
6. Protease Inhibitors in AIDS Therapy. Ogden RC, Flexner CW. Eds.). Marcel Dekker, New York, USA, 2011; pp.1-300.
7. Ghosh AK, Osswald HL, Prato G. Recent progress in the development of HIV-1 protease inhibitors for the treatment of HIV/AIDS. J Med Chem. 2016; 59:5172-5208.
8. Carpenter CC, Fischl MA, Hammer SM, Hirsch MS, Jacobsen DM, Katzenstein DA, Montaner JS, Richman DD, Saag MS, Schooley RT, Thompson MA, Vella S, Yeni PG, Volberding PA. Antiretroviral therapy for HIV infection in 1998: updated recommendations of the International AIDS Society-USA Panel. JAMA 1998; 280:78-86.
9. Moore RD, Chaisson RE. Natural history of HIV infection in the era of combination antiretroviral therapy. AIDS. 1999; 13:1933-1942.
10. Ghosh AK, Dawson ZL, Mitsuya H. Darunavir, a conceptually new HIV-1 protease inhibitor for the treatment of drug-resistant HIV. Bioorg Med Chem. 2007; 15:7576-7580.
11. Koh Y, Nakata H, Maeda K, *et al.* Novel bis-tetrahydrofuranylurethane-containing nonpeptidic protease inhibitor (PI) UIC-94017 (TMC114) with potent activity against multi-PI-resistant human immunodeficiency virus *in vitro*. Antimicrob Agents Chemother. 2003; 47:3123-3129.
12. Ivetac A, McCammon JA. Elucidating the inhibition mechanism of HIV-1 non-nucleoside reverse transcriptase inhibitors through multicopy molecular dynamics simulations. J Mol Biol. 2009; 388:644-658.
13. Jochmans D. Novel HIV-1 reverse transcriptase inhibitors. Virus Res. 2008; 134:171-185.
14. Moyle G. Stopping HIV fusion with enfuvirtide, the first step to extracellular HAART. J. Antimicrob Chemother. 2003: 51:213-217.
15. Maraviroc reduces viral load in naive patients at 48 weeks. AIDS Patient Care STDS. 2007; 21:703-704.
16. Métifiot M, Marchand C, Pommier Y. HIV integrase inhibitors: 20-year landmark and challenges. Adv Pharmacol. 2013; 67:75-105.
17. Messiaen P, Wensing AM, Fun A, Nijhuis M, Brusselaers N, Vandekerckhove L. Clinical use of HIV integrase inhibitors: a systematic review and meta-analysis. PLoS One. 2013; 8:e52562.
18. HIVinfo.NIH.gov. What to start: choosing an HIV treatment regimen. *https://hivinfo.nih.gov/understanding-hiv/fact-sheets/what-start-choosing-hiv-treatment-regimen* (accessed February 26, 2023).
19. Lewis W, Day BJ, Copeland WC. Mitochondrial toxicity of NRTI antiviral drugs: an integrated cellular perspective. Nat Rev Drug Discov. 2003; 2:812-822.
20. Venanzi Rullo E, Ceccarelli M, Condorelli F, Facciolà A, Visalli G, D'Aleo F, Paolucci I, Cacopardo B, Pinzone MR, Di Rosa M, Nunnari G, Pellicanò GF. Investigational drugs in HIV: Pros and cons of entry and fusion inhibitors (Review). Mol Med Rep. 2019; 19:1987-1995.
21. Ghosh AK, Anderson DD, Weber IT, Mitsuya H. Enhancing protein backbone binding-a fruitful concept for combating drug-resistant HIV. Angew Chem Int Ed Engl. 2012; 51:1778-1802.
22. Llibre JM, Pulido F, García F, García Deltoro M, Blanco JL, Delgado R. Genetic barrier to resistance for dolutegravir. AIDS Rev. 2015; 17:56-64.

Received February 28, 2023; Accepted March 10, 2023.

Released online in J-STAGE as advance publication March 22, 2023.

**Address correspondence to*:
Arun K. Ghosh, Department of Chemistry/ Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, West Lafayette, IN 47907, USA.
E-mail: akghosh@purdue.edu

Global Health & Medicine. 2023; 5(4):199-207 REVIEW
DOI: 10.35772/ghm.2023.01065

Biology of the hepatitis B virus (HBV) core and capsid assembly modulators (CAMs) for chronic hepatitis B (CHB) cure

William M. McFadden[1,2], Stefan G. Sarafianos[1,2,*]

[1] Center for ViroScience and Cure, Laboratory of Biochemical Pharmacology, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA;
[2] Children's Healthcare of Atlanta, Atlanta, GA, USA.

Abstract: Hepatitis B virus (HBV) is a hepadnavirus, a small DNA virus that infects liver tissue, with some unusual replication steps that share similarities to retroviruses. HBV infection can lead to chronic hepatitis B (CHB), a life-long infection associated with significant risks of liver disease, especially if untreated. HBV is a significant global health problem, with hundreds of millions currently living with CHB. Currently approved strategies to prevent or inhibit HBV are highly effective, however, a cure for CHB has remained elusive. To achieve a cure, elimination of the functionally integrated HBV covalently closed chromosomal DNA (cccDNA) genome is required. The capsid core is an essential component of HBV replication, serving roles when establishing infection and in creating new virions. Over the last two and a half decades, significant efforts have been made to find and characterize antivirals that target the capsid, specifically the HBV core protein (Cp). The antivirals that interfere with the kinetics and morphology of the capsid, termed capsid assembly modulators (CAMs), are extremely potent, and clinical investigations indicate they are well tolerated and highly effective. Several CAMs offer the potential to cure CHB by decreasing the cccDNA pools. Here, we review the biology of the HBV capsid, focused on Cp, and the development of inhibitors that target it.

***Keywords*:** HBV, capsid assembly modulators (CAMs), hepatitis, hepadnaviridae, capsid core

Introduction

The hepatitis B virus (HBV) was first discovered as an infectious agent in the 1960s by Dr. Baruch Blumberg, who described the presence of what would later be named the HBV surface antigen (HBsAg) in the blood of patients with hepatitis (*1*). Blumberg's discovery subsequently led to the development of diagnostic screening tests and effective vaccines against HBV by targeting HBsAg, work for which he would later be awarded the 1976 Nobel Prize in Physiology or Medicine (*2*). As of 2019, the World Health Organization (WHO) estimates that approximately 1.5 million new HBV infections occur each year, with the highest burden of disease currently in the WHO Western Pacific Region and the WHO African Region (*3*). A fraction of adults (< 10%) with acute HBV infection will develop chronic hepatitis B (CHB), while acutely infected infants are at a much higher risk (~90%); a staggering 296 million individuals are estimated to be living with CHB (*3,4*). Despite the goals set by the WHO to decrease HBV-related mortality by 65% from 2015 to 2030, global HBV-related mortality is projected to increase by 39% during this time (*5,6*). Many factors contribute to this increased mortality (recently reviewed (*6*)) including, for example, economic disparities in HBV distribution between and within countries, comorbidities and viral coinfections like hepatitis D virus and human immunodeficiency virus (HIV), and societal stigmas that add barriers to receiving HBV healthcare (*6,7*).

Currently approved strategies to prevent or inhibit HBV are highly effective, including the HBV vaccine (90–95% effective), as well as repurposed nucleos(t)ide analogs (NUCs) from HIV reverse transcriptase (RT) inhibitors like tenofovir and lamivudine (3TC) (*4,7,8*). Although HBV is effectively inhibited by NUCs, caseation of antiviral therapy leads to unpredictable outcomes and often a rebound of viral load (*9*). Thus, the current standard of care for CHB is life-long treatment with NUCs. There is another approved class with curative potential, interferon-α or pegylated interferon-α (peg-IFNα), but it is not well tolerated and suppresses chronic infection in only 30% of patients (*10*). Currently, CHB has no reliable cure. Therefore, direct-acting agents that target outside the polymerase, alone or in combination, are likely required to achieve HBV eradication (*11*).

The HBV replication cycle

The mature, infectious HBV virion is a 42 nm particle

comprised of a viral envelope with embedded HBsAg and contains the relaxed-circular DNA genome (rcDNA) that is covalently attached to the polymerase (P) and encapsulated by the assembled nucleocapsid core (*12,13*).

HBV belongs to the hepadnaviridae family of viruses, and as such HBV infects liver cells following HBsAg interactions with the sodium taurocholate cotransporting polypeptide (NTCP), a transmembrane protein specifically expressed in hepatocytes (*14*). The virus is internalized in an endosome, and the nucleocapsid is released into the cytoplasm by currently unresolved mechanisms (*15*). In infectious particles, the nucleocapsid is a T = 4 icosahedral core that is an assembly of the multimeric core protein (Cp), or HBV core antigen (HBcAg) (Figure 1). Once in the cytoplasm, the core is trafficked toward the nucleus to proceed through the nuclear pore complex (NPC) in an importin-dependent fashion (*12,16*). Following nuclear entry, the partially double-stranded and partially single-stranded rcDNA with the covalently attached P protein triggers host cell DNA repair mechanisms. This inevitably leads to the formation of the covalently closed chromosomal DNA (cccDNA), an episome indistinguishable to the host from its own genome, functionally integrating itself into the cell (*17,18*).

The cccDNA genome is the template for multiple mRNA transcripts of varying size, one of which encodes the full pre-genomic RNA (pgRNA) that can be translated into HBcAg or HBeAg depending on the ORF used, and P (*19-21*). The HBV P protein is a large, multifunctional protein with Ribonuclease H (RNaseH), RT protein-priming, RNA-dependent DNA-polymerase (RdDP) and DNA-dependent DNA-polymerase (DdDP) activity (*8,21*). The interaction of P with pgRNA, specifically with the epsilon RNA stem loop, is required for encapsidation into assembling cores, which has fine-tuned assembly kinetics to make infectious particles (*22*). The pgRNA serves as the template for RT when creating the rcDNA after encapsidation (*21,23*). In addition to the infectious virions, referred to as "Dane particles", infected cells excrete non-infectious soluble core antigens (HBeAg) and excrete HBsAg-coated subviral particles (SVP). These SVPs can contain viral mRNA, erroneous cellular mRNA or be entirely devoid of nucleic acid (*24*). The mRNA translated from cccDNA can be alternatively spliced, leading to production of small/medium and large HBsAg mRNA. The HBsAg precursor proteins are translated at the endoplasmic reticulum (ER) membrane, at different initiation codons, and adopt various conformations to enable the HBV envelope to form and bud (*12,19*).

The core protein (Cp) of HBV

The largest transcript from the cccDNA encodes the full HBV genome, the pgRNA. In addition to being packaged into assembling virions, as discussed above, the pgRNA can be used as the mRNA for multiple HBV proteins. pgRNA encodes for P, as well as two in-frame initiation codons that translate precore (p25) or Cp (p21) (*12,19,21*). When translated starting at the second in-frame initiation codon, Cp is cytosolically translated prior to its assembly into the HBV capsid core. Cp is a 21 kDa protein with 183–185 amino acids, depending on

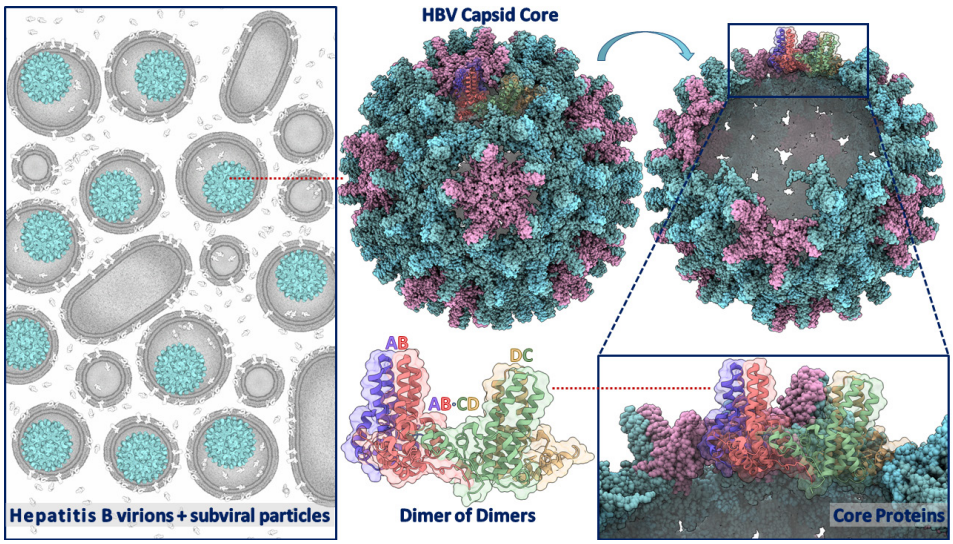


Figure 1. Structure of the hepatitis B Virus (HBV) capsid core. [Left] Rendition of released particles from HBV infection, including mature virions with assembled capsids (PDB: 6HTX) (*96*) and core protein (Cp) dimers (PDB: 6ECS) (*97*) as well as both non-infectious subviral particles and excreted HBV E Antigen (HBeAg, PDB: 3V6Z) (*51*). No full structure of HBV Surface Antigen (HBsAg) is deposited in the PDB; partial HBsAg (PDB: 7TUK) (*98*) and CD9 (PDB: 6K4J) (*99*) protein embedded in the default membrane structure from cellPAINT to represent the viral envelope (in grey). The mature capsid shown in blue and all other proteins in white. The P•pgRNA complex or P•rcDNA would be located inside the core. Made with cellPAINT (v2.0) (*100*). [Right] Two orientations of the HBV Capsid core (PDB: 6HTX) (*96*) with hexamers in cyan and pentamers in pink. One dimer of Cp dimers has the secondary structure shown with distinct colors in each Cp monomer to display protein·protein interactions. Made with ChimeraX (v1.5) (*101*).

the virus isolate. The N-terminal Domain of Cp (Cp_{NTD}) is responsible for capsid assembly and the C-terminal domain of Cp (Cp_{CTD}) is responsible for binding nucleic acid and signaling (*13,25-29*) (Figure 2A).

The Cp_{NTD} comprises residues 1–149 and, when expressed in *E. coli*, can assemble *in vitro* into particles indistinguishable from native HBV cores; however, the Cp_{NTD} could not assemble in mammalian cells or *in vitro* with rabbit reticulocyte lysate (*29-33*). This domain contains five α-helices (α1–α5), with α3 and α4 acting as the dimerization interface by making a 4-helix bundle (4HB) in Cp•Cp dimers, and α1, α2, and α5 sit perpendicular to the 4HB making the interface for dimer-dimer interactions (Figure 2B). Following translation, Cp monomers will immediately dimerize at the hairpins made by the amphipathic, antiparallel α3 and α4, forming a 4HB, which protrudes out of assembled cores like a spike (Figure 2C) (*25,29,30,34-36*). The 4HB is stabilized by a disulfide bond between the Cys61 in both monomers, but this linkage is not required for Cp assembly (*21,37*). Following dimerization, hydrophobic interactions between α5's and multiple contacts throughout Cp create dimer•dimer interactions to form the assembled capsid (*36,38,39*). The residues 140–149 are frequently referred to as a linker domain connecting Cp_{NTD} and Cp_{CTD}, and it has assembly-independent functions (*40,41*).

The Cp_{CTD} comprises residues 150–183 or 150–185 depending on subtype, and is characterized by intrinsic disorder, due in part to the presence of 16 positively charged Arg residues and 7 residues (6 Ser and 1 Thr) that can be phosphorylated in this 35–37 amino acid region (*26-28,42*) (Figure 2, C-E). These sequential Arg residues provide the nucleic acid binding functions of Cp that are needed for encapsulation of pgRNA during core assembly, as well as influencing rcDNA formation and Cp potentially being associated with nuclear cccDNA (*17,23,27-29,41,43)*. The Cp_{CTD} additionally contains both nuclear localization signals (NLS) and nuclear export signals (NES) that are made of these sequential Arg residues (*16*). Further, the phosphorylation of Cp_{CTD} residues encode a complex regulatory system that influences many aspects of HBV replication, including cellular trafficking, disassembly at the nuclear pore complex and RNA encapsidation, which remains the target of ongoing investigations (*27,31,32,44,45*). For many years, the full-length Cp protein was challenging to recombinantly express and purify; truncated expression constructs made only of the Cp_{NTD} gave increased stability, and thus, many studies of Cp assembly have relied solely on the Cp_{NTD}. Now, bacterial codon-optimized expression vectors allow for the efficient production of full-length Cp in *E. coli*, especially helping in the translation of the Arg-rich Cp_{CTD} (*28,45,46*). While the Cp_{CTD} is not required for capsid lattice assembly, it is required for creating infectious HBV virions (*47*).

Translation of the preCore (preC) begins at the

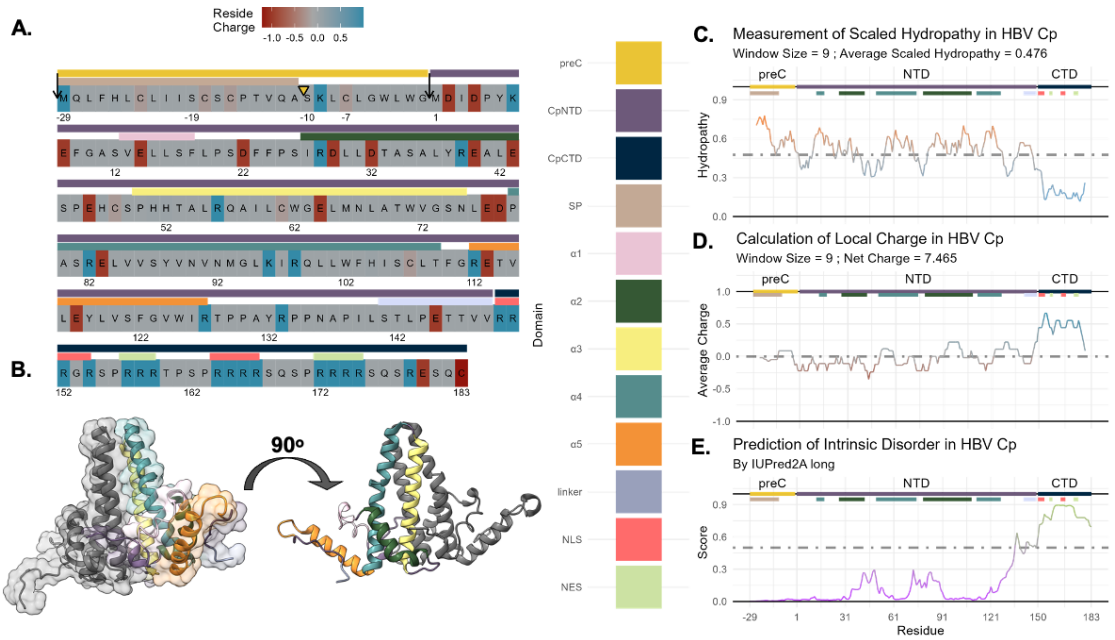


Figure 2. Structure and Characteristics of the HBV core protein (Cp). (A). Sequence and structural motifs in p25; colors to the right (UniProt: P0C6H5). Arrows indicate start codon sites, with the second being used to translate Cp and the first for preCore (preC). The site of the Signal Peptide (SP; brown) cleavage shown with the yellow triangle. Residues are colored by charges at pH 7.0 (*42*). **(B)**. Two Cp Dimers (PDB: 6HTX) (*96*), one in gray and the other colored based on the sequence annotation in (A). Made with ChimeraX (*101*). **(C)**. Shows the local hydropathy of the Cp, with the Cp_{NTD} hydrophobic helices for assembling the core. **(D)**. Displays the local charge of the Cp, exemplifying the Cp_{CTD} having a characteristic basic charge for nucleic acid binding. **(E)**. Predictions of intrinsic disorder by IUPred2 (> 0.5 disordered region; < 0.5 ordered region) (*102*), exemplifying the disordered nature of the Cp_{CTD}. A, C-E made with idpr v 1.8.0 (*42*).

initiation codon upstream of the Cp initiation site and generates a precursor protein that contains a 29 residue N-terminal extension of the Cp, which contains a cotranslational ER localization signal (*19,20*). A segment of the preC N-terminus is processed inside the ER lumen, changing the protein from p25 to p22, and subsequent processing at the C-terminus into p17 prior to ER-Golgi–mediated secretion (Figure 2A; yellow triangle) (*48,49*). The p22 intermediate and Cp are nearly identical at the sequence level, except for the remaining 10 residue N-terminal extension in p22 (*19,48,49*). This short leader sequence contains an influential cysteine residue (Cys-7), that forms a disulfide bond with Cys61, creating distinct quaternary structures that result in two HBV-related antigens: HBeAg and HBcAg for p17 and Cp, respectively (*13,50,51*). Of note, when denaturing Cp, the antigenic region of HBeAg is revealed (*49,52*). The function of HBeAg is not known and it is dispensable for infection; HBeAg is found in serum of patients shortly after infection and, as such, is used as a marker for active viral replication (*53*). Additionally, there is emerging interest in tracking the transcriptional activity of cccDNA using the hepatitis B virus core-related antigen (HBcrAg), a mixture of HBcAg, HBeAg, and other preC gene products (*19*).

Once the critical concentration of Cp has been surpassed, 90 or 120 Cp dimers will spontaneously self-assemble into T = 3 or T = 4 icosahedral capsids, respectively. In the assembled cores, the Cp_{NTD} faces outwards with the 4HB protrusions giving the capsid a spike-like appearance, and the Cp_{CTD} is generally localized to the interior and is highly flexible. Assembly is characterized by sigmoidal kinetics, similar to a crystal lattice with the rate-limiting step being the formation of a nucleation seed (*54*). The lag phase is characterized by the formation of a trimer of dimers; individual dimer-dimer interactions *in vitro* are weak (~3.5 kcal/mol), which allows for the thermodynamic editing of improperly associated dimers. Once nuclei form, they rapidly assemble into icosahedral capsids, as free dimers remain. Cp dimers form at least 3 contacts with additive association energies that are enough to form stable capsids even though individual dimer•dimer interactions are weak (*54-56*). It is important to note that the *in vivo* assembly also can utilize RNA not possible in these Cp_{NTD} constructs; in purified capsid-like particles, those with the Cp_{CTD} and ssRNA require harsher denaturation conditions (*45,47,57*). T = 4 capsids are the primary result of assembly products (> 90%) and have a diameter of ~36 nm, while T = 3 capsids have a diameter ~32 nm (*58*). The ratio of these core sizes, as well as the kinetics of assembly, are impacted by ionic strength and protein concentration with mild conditions favoring T = 4 and few intermediates (*28*). In addition to the spiked icosohedreon, the capsid is characterized by many holes that are permeable to ions, metabolites and inhibitors (*25,39,58*).

Capsid assembly modulators (CAMs)

A class of molecules with curative potential are CAMs that bind Cp dimers. Also referred to as core protein allosteric modulators (CpAMs) and Capsid Inhibitors (CIs), these are an exciting development in the field of HBV therapeutics, as NUCs treat but do not cure CHB (*59*). These Cp-targeting HBV antivirals bind to the same site but are commonly subdivided into two classes: type I CAMs that create **a**ggregated or **a**berrant capsids that are unable to function (CAM-**A**), and type II CAMs that enhance the assembly rates of Cp dimer•dimer interactions to make **e**mpty cores (CAM-**E**) (*28,60,61*). As the capsid has numerous roles throughout the replication cycle, its misassembly can impact multiple steps in acute or CHB infection.

Class I: CAM-A

The first CAM-A molecule described was BAY 41-4109, belonging to the heteroaryldihydropyrimidines (HAP) family with HBV inhibition at submicromolar concentrations (*33,62,63*). Oral administration of BAY 41-4109 decreased HBV DNA in liver and plasma of HBV-transgenic mice, in line with 3TC treatment, but also showed a reduction of cytoplasmic HBcAg, a phenotype distinct from the NUC treatment (*62*). The observed Cp reduction is a result of proteosome activity (*63*), although an increase in Cp ubiquitylation has not been shown following HAP treatment (*33*). More recent studies have found nuclear aggregates of Cp, specifically associated with promyelocytic leukemia (PML) nuclear bodies, after multiple days of CAM-A (BAY 41-4109 and BAY 38-7690) but not CAM-E treatment (*64,65*). Shortly after BAY 41-4109 treatment, Cp aggregates were primarily cytoplasmic, but associated with nuclear envelope (*66*). Further, it was shown that after infection BAY 41-4109–induced Cp aggregates were perinuclear and targeted for p62-mediated macroautophagy and lysosomal degradation by the host factor STUB1, an E3 ubiquitin ligase (*67*). It should be noted that STUB1 is a co-chaperone of heat shock protein 70 (HSP70) and HSP90 (*68*), and both are considered proviral factors for HBV capsid assembly (*67,69,70*). Though the BAY compounds were not clinically developed, they have served as good probes to characterize the CAM-A chemotype.

Currently, the most promising HAP compounds are RO7049389 and GLS4. RO7049389 is currently in phase 2 trials (NCT04225715), with phase 1 results (NCT02952924) showing infrequent, mild adverse events and a reduction of HBV DNA in treatment-naïve CHB patients after 4 weeks of CAM-A administration comparable to NUC controls (*71*). Additionally, due to the high prevalence of HBV in Asia (*3,6*), the safety of RO7049389 was validated in healthy Chinese volunteers in a phase 1 clinical trial (NCT03570658). This showed

the compound was well-tolerated in single (600 mg) and multiple (400 mg twice daily) doses, and the safety profiles were similar between Asian and non-Asian healthy volunteers, though with higher plasma exposure of RO7049389 observed in the Chinese participants (*72*). The other leading CAM-A molecule currently in phase 2 trials is GLS4 (NCT04147208), a derivative of Bay 39-5493, with nanomolar potency and is fairly well-tolerated and effective when administered at 120 mg daily in combination with 100 mg ritonavir for 28 days (*73,74*). The safety and efficacy of these CAM-A compounds are exciting, but their long-term application and antiviral resistance remains to be seen.

Some other CAM-A molecules include KL060332 (*75*), a HAP molecule under a phase 1a trial in China, and preclinical compounds JNJ-890 (*76*), HAP_R01 (*77*), and ZW-1847 (*78*). A unique, non-HAP molecule with CAM-A phenotype is Ciclopirox, which inhibited HBV at 5 mg/kg in mice (*79*). Interestingly, ciclopirox olamine®, an antifungal agent, was tested for oral safety and tolerability as an anti-apoptotic gene suppressant for treating hematological malignancies (NCT00990587), indicating its safety for use in future trials investigating HBV inhibition in clinical trials (*79,80*).

Class II: CAM-E

Both CAM-A and CAM-E bind to the same hydrophobic pocket at Cp dimer•dimer interfaces, but the cores formed following only CAM-E treatment are noninfectious, vacant icosahedral capsids. CAM-E molecules enhance the rate dimer-dimer interactions, overcoming the rate-limiting step in assembly, and form icosahedral capsids that are devoid of P•pgRNA. Unlike the CAM-A class made primarily of the HAP chemotype that results in aggregates, CAM-E molecules are much more diverse and rapidly lead to native-like assemblies. Some CAM-E scaffolds include phenylpropenamides (PPAs), glyoxamoylpyrroloxamides (GLPs), sulfamoylbenzamides (SBAs), and sulfamoylpyrroloamides (SPAs).

One of first reported CAMs and the best studied CAM-E molecule is AT-130, which belongs to the PPA class (*61,81*). AT-130 inhibits HBV with submicromolar potency in cell culture but has not been tried in clinical trials. As the prototypical scaffold for the CAM-E chemotype, AT-130 has been shown to increase the kinetics of capsid assembly through interactions near Cp_{NTD} linker and α5 that alter the interface of dimer•dimer interactions, as well as distorting the 4HB, resulting in intermediates that are primed to assemble (*82-84*). These result in icosahedral capsids without the P•pgRNA needed for HBV replication, or partially completed assembly intermediates (*84,85*).

Another preclinical CAM-E class that has great potential is the GLP class, with the first GLP compound patented in 2015 (*61,86*). GLP compounds are exceptionally potent, with the compound GLP-26 having nanomolar potency in humanized mice (*87*). GLP-26 was further shown to be well tolerated and highly effective at inhibiting HBV in both non-human primate studies and primary human cardiomyocytes, indicating safety for further investigations (*88*).

Both the SBA and SPA classes are some of the most clinically developed CAMs. One of the first successful clinical investigations into CAM safety was the SBA compound NVR 3-778 (NCT02401737), which was tolerated but not as effective as approved NUCs and thus was discontinued (*28,89*). An SBA under clinical investigation is JNJ-64530440 (phase 1b, NCT03439488) with potent antiviral activity in patients with CHB and was well tolerated (*90*). Additionally, the SPA JNJ-6379 (JADE NCT03361956), recently reported phase 2 trials results of a reduction in HBV DNA and RNA when given in combination with a NUC. They note that multiple patients had the T33N mutation emerge during monotherapy (*91*). This underscores the likely importance of combination therapy in future HBV therapeutics.

Some other promising CAM-Es molecules include ALG-000184, a potent inhibitor with successful phase 1 trials (NCT04536337) (*92*), Canocapavir (ZM-H1505R) that was well tolerated (Phase 1b, NCT05470829) (*93*), and GST-HG141 (phase 1, NCT04386915 & NCT04868981) (*94*). Many CAMs have been reported and are under investigation in clinical trials without their exact CAM phenotype described (Recently reviewed (*28,55*)). Additionally, a novel HBV antiviral class has been reported as a cccDNA inhibitor; the molecule ccc_R08 is hypothesized to target an unknown host factor and decreased preexisting cccDNA pools, unlike currently reported CAMs (*95*).

Conclusions

At the present, approximately 3.5% of the world's population lives with CHB, though most are unaware (*3,6*). Key to curing CHB is elimination of cccDNA, and the currently approved and widely used NUCs suppress HBV replication but do not achieve a cure (*18,55*). Due to their ability to clear cccDNA, CAMs that modify Cp dimer•dimer interactions have the potential to redefine the standard of care for treating HBV infection and could subsequently achieve a cure for CHB (*11,59*). The long-term effects of CAM treatment and likely emergence of CAM-induced antiviral resistance remain to be investigated. However, the progress in CAM development and successful investigations into HBV capsid biology over the last two and a half decades give promise for highly effective and well characterized treatments to potentially cure the hundreds of millions currently living with CHB.

Funding: This research was supported in part by the

National Institutes of Health (R01 AI132833 and R01 AI121315 to SGS; WMM was supported in part by T32 GM135060 and F31 AI174951). SGS acknowledges funding from the Nahmias-Schinazi Distinguished Chair in Research.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Blumberg B, Sutnick A, London WT. Hepatitis and leukemia: their relation to Australia antigen. Bull N Y Acad Med. 1968; 44:1566-1586.
2. Suk-Fong Lok A. Hepatitis B: 50 years after the discovery of Australia antigen. J Viral Hepat. 2016; 23:5-14.
3. World Health Organization. Hepatitis B: WHO; 2022. *https://www.who.int/news-room/fact-sheets/detail/hepatitis-b* (accessed May 15, 2023)
4. Indolfi G, Easterbrook P, Dusheiko G, Siberry G, Chang MH, Thorne C, Bulterys M, Chan PL, El-Sayed MH, Giaquinto C, Jonas MM, Meyers T, Walsh N, Wirth S, Penazzato M. Hepatitis B virus infection in children and adolescents. Lancet Gastroenterol Hepatol. 2019; 4:466-476.
5. Razavi-Shearer D, Blach S, Gamkrelidze I, Estes C, Mooneyhan E, Razavi-Shearer K, Razavi H. The disease burden of hepatitis B and hepatitis C from 2015 to 2030: the long and winding road. Journal of Hepatology. 2022; 77:S43.
6. Hsu YC, Huang DQ, Nguyen MH. Global burden of hepatitis B virus: current status, missed opportunities and a call for action. Nat Rev Gastroenterol Hepatol. 2023. doi: 10.1038/s41575-023-00760-9.
7. Cooke GS, Andrieux-Meyer I, Applegate TL, *et al*. Accelerating the elimination of viral hepatitis. Lancet Gastroenterol Hepatol. 2019; 4:135-184.
8. Michailidis E, Kirby KA, Hachiya A, Yoo W, Hong SP, Kim SO, Folk WR, Sarafianos SG. Antiviral therapies: focus on hepatitis B reverse transcriptase. Int J Biochem Cell Biol. 2012; 44:1060-1071.
9. Pockros PJ, Mulgaonkar A. Cessation of nucleoside/nucleotide analogue therapy in chronic hepatitis B HBeAg-negative patients. Gastroenterol Hepatol (N Y). 2022; 18:320-325.
10. Ye J, Chen J. Interferon and hepatitis B: current and future perspectives. Front Immunol. 2021; 12:733364.
11. Boucle S, Bassit L, Ehteshami M, Schinazi RF. Toward elimination of hepatitis B virus using novel drugs, approaches, and combined modalities. Clin Liver Dis. 2016; 20:737-749.
12. Tsukuda S, Watashi K. Hepatitis B virus biology and life cycle. Antiviral Res. 2020; 182:104925.
13. Selzer L, Zlotnick A. Assembly and release of hepatitis B virus. Cold Spring Harb Perspect Med. 2015; 5:a021394.
14. Yan H, Zhong G, Xu G, *et al*. Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus. Elife. 2012; 1:e00049.
15. Herrscher C, Roingeard P, Blanchard E. Hepatitis B virus entry into cells. Cells. 2020; 9:1486.
16. Li HC, Huang EY, Su PY, Wu SY, Yang CC, Lin YS, Chang WC, Shih C. Nuclear Export and import of human hepatitis B virus capsid protein and particles. PLoS Pathog. 2010; 6:e1001162.
17. Bock CT, Schwinn S, Locarnini S, Fyfe J, Manns MP, Trautwein C, Zentgraf H. Structural organization of the hepatitis B virus minichromosome. J Mol Biol. 2001; 307:183-196.
18. Wei L, Ploss A. Mechanism of hepatitis B virus cccDNA formation. Viruses. 2021; 13:1463.
19. Hong X, Luckenbaugh L, Mendenhall M, Walsh R, Cabuang L, Soppe S, Revill PA, Burdette D, Feierbach B, Delaney W, Hu J. Characterization of hepatitis B precore/core-related antigens. J Virol. 2021; 95:e01695-e01720.
20. Standring DN, Ou JH, Masiarz FR, Rutter WJ. A signal peptide encoded within the precore region of hepatitis B virus directs the secretion of a heterogeneous population of e antigens in Xenopus oocytes. Proc Natl Acad Sci U S A. 1988; 85:8405-8409.
21. Clark DN, Tajwar R, Hu J, Tavis JE. The hepatitis B virus polymerase. Enzymes. 2021; 50:195-226.
22. Bartenschlager R, Schaller H. Hepadnaviral assembly is initiated by polymerase binding to the encapsidation signal in the viral RNA genome. EMBO J. 1992; 11:3413-3420.
23. Nassal M. The arginine-rich domain of the hepatitis B virus core protein is required for pregenome encapsidation and productive viral positive-strand DNA synthesis but not for virus assembly. J Virol. 1992; 66:4107-4116.
24. Chai N, Chang HE, Nicolas E, Han Z, Jarnik M, Taylor J. Properties of subviral particles of hepatitis B virus. J Virol. 2008; 82:7812-7817.
25. Wynne SA, Crowther RA, Leslie AG. The crystal structure of the human hepatitis B virus capsid. Mol Cell. 1999; 3:771-780.
26. Chain BM, Myers R. Variability and conservation in hepatitis B virus core protein. BMC Microbiology. 2005; 5:33.
27. de Rocquigny H, Rat V, Pastor F, Darlix JL, Hourioux C, Roingeard P. Phosphorylation of the arginine-rich C-terminal domains of the hepatitis B virus (HBV) core protein as a fine regulator of the interaction between HBc and nucleic acid. Viruses. 2020; 12:738.
28. Niklasch M, Zimmermann P, Nassal M. The hepatitis B virus nucleocapsid–dynamic compartment for infectious virus production and new antiviral target. Biomedicines. 2021; 9:1577.
29. Birnbaum F, Nassal M. Hepatitis B virus nucleocapsid assembly: primary structure requirements in the core protein. J Virol. 1990; 64:3319-3330.
30. Wingfield PT, Stahl SJ, Williams RW, Steven AC. Hepatitis core antigen produced in escherichia coli: subunit composition, conformation analysis, and *in vitro* capsid assembly. Biochemistry. 1995; 34:4919-4932.
31. Ludgate L, Liu K, Luckenbaugh L, Streck N, Eng S, Voitenleitner C, Delaney WE 4th, Hu J. Cell-free hepatitis B virus capsid assembly dependent on the core protein C-terminal domain and regulated by phosphorylation. J Virol. 2016; 90:5830-5844.
32. Rat V, Pinson X, Seigneuret F, Durand S, Herrscher C, Lemoine R, Burlaud-Gaillard J, Raynal PY, Hourioux C, Roingeard P, Tramier M, de Rocquigny H. Hepatitis B virus core protein domains essential for viral capsid assembly in a cellular context. J Mol Biol. 2020; 432:3802-3819.
33. Kim H, Ko C, Lee JY, Kim M. Current progress in the development of hepatitis B virus capsid assembly modulators: chemical structure, mode-of-action and

efficacy. Molecules. 2021; 26:7420.
34. Conway JF, Cheng N, Zlotnick A, Wingfield PT, Stahl SJ, Steven AC. Visualization of a 4-helix bundle in the hepatitis B virus capsid by cryo-electron microscopy. Nature. 1997; 386:91-94.
35. Böttcher B, Wynne SA, Crowther RA. Determination of the fold of the core protein of hepatitis B virus by electron cryomicroscopy. Nature. 1997; 386:88-91.
36. Zheng CL, Fu YM, Xu ZX, Zou Y, Deng K. Hepatitis B virus core protein dimer*dimer interface is critical for viral replication. Mol Med Rep. 2019; 19:262-270.
37. Bourne CR, Finn MG, Zlotnick A. Global structural changes in hepatitis B virus capsids induced by the assembly effector HAP1. J Virol. 2006; 80:11055-11061.
38. Zhao Z, Wang JC, Segura CP, Hadden-Perilla JA, Zlotnick A. The integrity of the intradimer interface of the hepatitis B virus capsid protein dimer regulates capsid self-assembly. ACS Chem Biol. 2020; 15:3124-3132.
39. Hadden JA, Perilla JR, Schlicksup CJ, Venkatakrishnan B, Zlotnick A, Schulten K. All-atom molecular dynamics of the HBV capsid reveals insights into biological function and cryo-EM resolution limits. Elife. 2018; 7:e32478.
40. Watts NR, Conway JF, Cheng N, Stahl SJ, Belnap DM, Steven AC, Wingfield PT. The morphogenic linker peptide of HBV capsid protein forms a mobile array on the interior surface. EMBO J. 2002; 21:876-884.
41. Xi J, Luckenbaugh L, Hu J. Multiple roles of PP2A binding motif in hepatitis B virus core linker and PP2A in regulating core phosphorylation state and viral replication. PLoS Pathog. 2021; 17:e1009230.
42. McFadden WM, Yanowitz JL. idpr: a package for profiling and analyzing intrinsically disordered proteins in R. PLoS One. 2022; 17:e0266929.
43. Zlotnick A, Cheng N, Stahl SJ, Conway JF, Steven AC, Wingfield PT. Localization of the C terminus of the assembly domain of hepatitis B virus capsid protein: implications for morphogenesis and organization of encapsidatedRNA. Proc Natl Acad Sci U S A. 1997; 94:9556-9561.
44. Luo J, Xi J, Gao L, Hu J. Role of hepatitis B virus capsid phosphorylation in nucleocapsid disassembly and covalently closed circular DNA formation. PLoS Pathog. 2020; 16:e1008459.
45. Heger-Stevic J, Zimmermann P, Lecoq L, Böttcher B, Nassal M. Hepatitis B virus core protein phosphorylation: Identification of the SRPK1 target sites and impact of their occupancy on RNA binding and capsid structure. PLoS Pathog. 2018; 14:e1007488.
46. Heger-Stevic J, Kolb P, Walker A, Nassal M. Displaying whole-chain proteins on hepatitis B virus capsid-like particles. Methods Mol Biol. 2018; 1776:503-531.
47. Chua PK, Tang FM, Huang JY, Suen CS, Shih C. Testing the balanced electrostatic interaction hypothesis of hepatitis B virus DNA synthesis by using an *in vivo* charge rebalance approach. J Virol. 2010; 84:2340-2351.
48. Messageot F, Salhi S, Eon P, Rossignol JM. Proteolytic processing of the hepatitis B virus e antigen precursor. Cleavage at two furin consensus sequences. J Biol Chem. 2003; 278:891-895.
49. Ito K, Kim KH, Lok AS, Tong S. Characterization of genotype-specific carboxyl-terminal cleavage sites of hepatitis B virus e antigen precursor and identification of furin as the candidate enzyme. J Virol. 2009; 83:3507-3517.
50. Nassal M, Rieger A. An intramolecular disulfide bridge between Cys-7 and Cys61 determines the structure of the secretory core gene product (e antigen) of hepatitis B virus. J Virol. 1993; 67:4307-4315.
51. DiMattia MA, Watts NR, Stahl SJ, Grimes JM, Steven AC, Stuart DI, Wingfield PT. Antigenic switching of hepatitis B virus by alternative dimerization of the capsid protein. Structure. 2013; 21:133-142.
52. Takahashi K, Akahane Y, Gotanda T, Mishiro T, Imai M, Miyakawa Y, Mayumi M. Demonstration of hepatitis B e antigen in the core of Dane particles. J Immunol. 1979; 122:275-279.
53. Guvenir M, Arikan A. Hepatitis B virus: from diagnosis to treatment. Pol J Microbiol. 2020; 69:391-399.
54. Zlotnick A. Theoretical aspects of virus capsid assembly. J Mol Recognit. 2005; 18:479-490.
55. Viswanathan U, Mani N, Hu Z, Ban H, Du Y, Hu J, Chang J, Guo JT. Targeting the multifunctional HBV core protein as a potential cure for chronic hepatitis B. Antiviral Res. 2020; 182:104917.
56. Ceres P, Zlotnick A. Weak protein-protein interactions are sufficient to drive assembly of hepatitis B virus capsids. Biochemistry. 2002; 41:11525-11531.
57. Porterfield JZ, Dhason MS, Loeb DD, Nassal M, Stray SJ, Zlotnick A. Full-length hepatitis B virus core protein packages viral and heterologous RNA with similarly high levels of cooperativity. J Virol. 2010; 84:7174-7184.
58. Crowther RA, Kiselev NA, Böttcher B, Berriman JA, Borisova GP, Ose V, Pumpens P. Three-dimensional structure of hepatitis B virus core particles determined by electron cryomicroscopy. Cell. 1994; 77:943-950.
59. Lam AM, Ren S, Espiritu C, Kelly M, Lau V, Zheng L, Hartman GD, Flores OA, Klumpp K. Hepatitis B virus capsid assembly modulators, but not nucleoside analogs, inhibit the production of extracellular pregenomic RNA and spliced RNA variants. Antimicrob Agents Chemother. 2017; 61:e00680-e00717.
60. McFadden WM, Sarafianos SG. Targeting the HIV-1 and HBV capsids, an encore. Viruses. 2023; 15:896.
61. Nijampatnam B, Liotta DC. Recent advances in the development of HBV capsid assembly modulators. Curr Opin Chem Biol. 2019; 50:73-79.
62. Weber O, Schlemmer KH, Hartmann E, Hagelschuer I, Paessens A, Graef E, Deres K, Goldmann S, Niewoehner U, Stoltefuss J, Haebich D, Ruebsamen-Waigmann H, Wohlfeil S. Inhibition of human hepatitis B virus (HBV) by a novel non-nucleosidic compound in a transgenic mouse model. Antiviral Res. 2002; 54:69-78.
63. Deres K, Schröder CH, Paessens A, *et al.* Inhibition of hepatitis B virus replication by drug-induced depletion of nucleocapsids. Science. 2003; 299:893-896.
64. Huber AD, Wolf JJ, Liu D, Gres AT, Tang J, Boschert KN, Puray-Chavez MN, Pineda DL, Laughlin TG, Coonrod EM, Yang Q, Ji J, Kirby KA, Wang Z, Sarafianos SG. The heteroaryldihydropyrimidine bay 38-7690 induces hepatitis B virus core protein aggregates associated with promyelocytic leukemia nuclear bodies in infected cells. mSphere. 2018; 3:e00131-e00218.
65. Corcuera A, Stolle K, Hillmer S, Seitz S, Lee JY, Bartenschlager R, Birkmann A, Urban A. Novel non-heteroarylpyrimidine (HAP) capsid assembly modifiers have a different mode of action from HAPs *in vitro*. Antiviral Res. 2018; 158:135-142.
66. Rat V, Seigneuret F, Burlaud-Gaillard J, Lemoine R, Hourioux C, Zoulim F, Testoni B, Meunier JC, Tauber C, Roingeard P, de Rocquigny H. BAY 41-4109-mediated

aggregation of assembled and misassembled HBV capsids in cells revealed by electron microscopy. Antiviral Res. 2019; 169:104557.
67. Lin J, Yin L, Xu XZ, Sun HC, Huang ZH, Ni XY, Chen Y, Lin X. Bay41-4109-induced aberrant polymers of hepatitis b capsid proteins are removed *via* STUB1-promoted p62-mediated macroautophagy. PLoS Pathog. 2022; 18:e1010204.
68. Kundrat L, Regan L. Balance between folding and degradation for Hsp90-dependent client proteins: a key role for CHIP. Biochemistry. 2010; 49:7428-7438.
69. Lim SO, Park SG, Yoo JH, Park YM, Kim HJ, Jang KT, Cho JW, Yoo BC, Jung GH, Park CK. Expression of heat shock proteins (HSP27, HSP60, HSP70, HSP90, GRP78, GRP94) in hepatitis B virus-related hepatocellular carcinomas and dysplastic nodules. World J Gastroenterol. 2005; 11:2072-2079.
70. Seo HW, Seo JP, Jung G. Heat shock protein 70 and heat shock protein 90 synergistically increase hepatitis B viral capsid assembly. Biochem Biophys Res Commun. 2018; 503:2892-2898.
71. Yuen MF, Zhou X, Gane E, Schwabe C, Tanwandee T, Feng S, Jin Y, Triyatni M, Lemenuel-Diot A, Cosson V, Xue Z, Kazma R, Bo Q. Safety, pharmacokinetics, and antiviral activity of RO7049389, a core protein allosteric modulator, in patients with chronic hepatitis B virus infection: a multicentre, randomised, placebo-controlled, phase 1 trial. Lancet Gastroenterol Hepatol. 2021; 6:723-732.
72. Wu X, Feng S, Zhang J, Zhang W, Zhang Y, Zhu M, Triyatni M, Zhao N, Bo Q, Jin Y. Evaluation of the safety, tolerability, and pharmacokinetics of RO7049389 in healthy Chinese volunteers. Clin Transl Sci. 2022; 15:195-203.
73. Zhang H, Wang F, Zhu X, Chen Y, Chen H, Li X, Wu M, Li C, Liu J, Zhang Y, Ding Y, Niu J. Antiviral activity and pharmacokinetics of the hepatitis B virus (HBV) capsid assembly modulator GLS4 in patients with chronic HBV infection. Clin Infect Dis. 2021; 73:175-182.
74. Ren Q, Liu X, Luo Z, Li J, Wang C, Goldmann S, Zhang J, Zhang Y. Discovery of hepatitis B virus capsid assembly inhibitors leading to a heteroaryldihydropyrimidine based clinical candidate (GLS4). Bioorg Med Chem. 2017; 25:1042-1056.
75. Tai Z, Tian Q, Zhao X, Xie J, Lu Y, Tan Y, Zhao W, Ma X, Yuan X, Song H, Xue T, Wang J. Discovery of KL060332, a potential best-in-class HBV capsid inhibitor. In The Liver Meeting Digital Experience™. *https://aasld.confex.com/aasld/2020/meetingapp.cgi/Paper/19680* (accessed May 15, 2023)
76. Lahlali T, Berke JM, Vergauwen K, Foca A, Vandyck K, Pauwels F, Zoulim F, Durantel D. Novel potent capsid assembly modulators regulate multiple steps of the hepatitis B virus life cycle. Antimicrob Agents Chemother. 2018; 62:e00835-e00918.
77. Qiu Z, Lin X, Zhang W, *et al*. Discovery and pre-clinical characterization of third-generation 4-H heteroaryldihydropyrimidine (HAP) analogues as hepatitis B virus (HBV) capsid inhibitors. J Med Chem. 2017; 60:3352-3371.
78. Senaweera S, Du H, Zhang H, Kirby KA, Tedbury PR, Xie J, Sarafianos SG, Wang Z. Discovery of new small molecule hits as hepatitis B virus capsid assembly modulators: structure and pharmacophore-based approaches. Viruses. 2021; 13:770.
79. Kang JA, Kim S, Park M, Park HJ, Kim JH, Park S, Hwang JR, Kim YC, Jun Kim Y, Cho Y, Sun Jin M, Park SG. Ciclopirox inhibits hepatitis B virus secretion by blocking capsid assembly. Nat Commun. 2019; 10:2184.
80. Minden MD, Hogge DE, Weir SJ, *et al*. Oral ciclopirox olamine displays biological activity in a phase I study in patients with advanced hematologic malignancies. Am J Hematol. 2014; 89:363-368.
81. Delaney WE, Edwards R, Colledge D, Shaw T, Furman P, Painter G, Locarnini S. Phenylpropenamide derivatives AT-61 and AT-130 inhibit replication of wild-type and lamivudine-resistant strains of hepatitis B virus *in vitro*. Antimicrob Agents Chemother. 2002; 46:3057-3060.
82. Pérez-Segura C, Goh BC, Hadden-Perilla JA. All-atom MD simulations of the HBV capsid complexed with AT130 reveal secondary and tertiary structural changes and mechanisms of allostery. Viruses. 2021; 13:564.
83. Katen SP, Tan Z, Chirapu SR, Finn MG, Zlotnick A. Assembly-directed antivirals differentially bind quasiequivalent pockets to modify hepatitis B virus capsid tertiary and quaternary structure. Structure. 2013; 21:1406-1416.
84. Kondylis P, Schlicksup CJ, Katen SP, Lee LS, Zlotnick A, Jacobson SC. Evolution of intermediates during capsid assembly of hepatitis B virus with phenylpropenamide-based antivirals. ACS Infect Dis. 2019; 5:769-777.
85. Feld JJ, Colledge D, Sozzi V, Edwards R, Littlejohn M, Locarnini SA. The phenylpropenamide derivative AT-130 blocks HBV replication at the level of viral RNA packaging. Antiviral Res. 2007; 76:168-177.
86. Vandyck K, Kesteleyn BRR, Pieters SMA, Rombouts G, Verschueren WG, Raboisson PJ-MB. Glyoxamide substituted pyrrolamide derivatives and the use thereof as medicaments for the treatment of hepatitis B. U.S. Patent 10,450,270[P]. 2019-10-22.
87. Amblard F, Boucle S, Bassit L, *et al*. Novel hepatitis B virus capsid assembly modulator induces potent antiviral responses *in vitro* and in humanized mice. Antimicrob Agents Chemother. 2020; 64:e01701-e01719.
88. Hurwitz SJ, McBrearty N, Arzumanyan A, Bichenkov E, Tao S, Bassit L, Chen Z, Kohler JJ, Amblard F, Feitelson MA, Schinazi RF. Studies on the efficacy, potential cardiotoxicity and monkey pharmacokinetics of GLP-26 as a potent hepatitis B virus capsid assembly modulator. Viruses. 2021; 13:114.
89. Gane EJ, Schwabe C, Walker K, Flores L, Hartman GD, Klumpp K, Liaw S, Brown N. Phase 1a safety and pharmacokinetics of NVR 3-778, a potential first-in-class HBV core inhibitor: LB-19. Hepatology. 2014; 60:1279A.
90. Gane EJ, Schwabe C, Berliba E, Tangkijvanich P, Jucov A, Ghicavii N, Verbinnen T, Lenz O, Talloen W, Kakuda TN, Westland C, Patel M, Yogaratnam JZ, Dragone L, Van Remoortere P. Safety, antiviral activity and pharmacokinetics of JNJ-64530440, a novel capsid assembly modulator, as 4 week monotherapy in treatment-naive patients with chronic hepatitis B virus infection. J Antimicrob Chemother. 2022; 77:1102-1110.
91. Janssen HLA, Hou J, Asselah T, *et al*. Randomised phase 2 study (JADE) of the HBV capsid assembly modulator JNJ-56136379 with or without a nucleos(t)ide analogue in patients with chronic hepatitis B infection. Gut. 2023; 72:1385-1398.
92. Yuen RMF, Agarwal K, Gane EJ, *et al*. Safety, pharmacokinetics, and antiviral activity of the class II

capsid assembly modulator ALG-000184 in subjects with chronic hepatitis B. Poster Presentation (SAT835). The International Liver Congress 2022, 22-26 June 2022. Journal of Hepatology, v. 77 n. S1, p. S835-836.
93. Jia H, Mai J, Wu M, *et al*. Safety, tolerability, pharmacokinetics, and antiviral activity of the novel core protein allosteric modulator ZM-H1505R (Canocapavir) in chronic hepatitis B patients: a randomized multiple-dose escalation trial. BMC Medicine. 2023; 21:98.
94. Li C, Wu M, Zhang H, Mai J, Yang L, Ding Y, Niu J, Mao J, Wu W, Zhang D, Tang Y, Yan W. Safety, tolerability, and pharmacokinetics of the novel hepatitis B virus capsid assembly modulator GST-HG141 in healthy Chinese subjects: a first-in-human single- and multiple-dose escalation trial. Antimicrob Agents Chemother. 2021; 65:e01220-e01221.
95. Wang L, Zhu Q, Zhang JD, *et al*. Discovery of a first-in-class orally available HBV cccDNA inhibitor. J Hepatol. 2023; 78:742-753.
96. Böttcher B, Nassal M. Structure of mutant hepatitis B core protein capsids with premature secretion phenotype. J Mol Biol. 2018; 430:4941-4954.
97. Zhao Z, Wang JC, Gonzalez-Gutierrez G, Venkatakrishnan B, Asor R, Khaykelson D, Raviv U, Zlotnick A. Structural differences between the woodchuck hepatitis virus core protein in the dimer and capsid states are consistent with entropic and conformational regulation of assembly. J Virol. 2019; 93:e00141-19.
98. Liu H, Hong X, Xi J, Menne S, Hu J, Wang JC. Cryo-EM structures of human hepatitis B and woodchuck hepatitis virus small spherical subviral particles. Sci Adv. 2022; 8:eabo4184.
99. Umeda R, Satouh Y, Takemoto M, Nakada-Nakura Y, Liu K, Yokoyama T, Shirouzu M, Iwata S, Nomura N, Sato K, Ikawa M, Nishizawa T, Nureki O. Structural insights into tetraspanin CD9 function. Nat Commun. 2020; 11:1606.
100. Gardner A, Autin L, Barbaro B, Olson AJ, Goodsell DS. CellPAINT: Interactive Illustration of Dynamic Mesoscale Cellular Environments. IEEE Comput Graph Appl. 2018; 38:51-66.
101. Pettersen EF, Goddard TD, Huang CC, Meng EC, Couch GS, Croll TI, Morris JH, Ferrin TE. UCSF chimeraX: structure visualization for researchers, educators, and developers. Protein Science. 2021; 30:70-82.
102. Mészáros B, Erdős G, Dosztányi Z. IUPred2A: context-dependent prediction of protein disorder as a function of redox state and protein binding. Nucleic Acids Res. 2018; 46:W329-W337.

Received May 22, 2023; Revised June 3, 2023; Accepted June 30, 2023.

Released online in J-STAGE as advance publication July 20, 2023.

**Address correspondence to*:
Stefan G. Sarafianos, Center for ViroScience and Cure, Laboratory of Biochemical Pharmacology, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA 30322, USA.
E-mail: stefanos.sarafianos@emory.edu

Global Health & Medicine. 2023; 5(4):208-215. REVIEW
DOI: 10.35772/ghm.2023.01014

Current status of and future perspectives on care for cancer survivors in China

Jie Song[1,§], Ruijia Li[1,§], Xiaojing Hu[1], Gang Ding[2], Minxing Chen[1,*], Chunlin Jin[1,*]

[1] Shanghai Health Development Research Center, Shanghai Medical Information Center, Shanghai, China;
[2] Oncology Department, Shanghai International Medical Center, Shanghai, China.

Abstract: Cancer is currently a major public health issue faced by countries around the world. With the progress of medical science and technology, the survival rate of cancer patients has increased significantly and the survival time has been effectively prolonged. How to provide quality and efficient care for the increasingly large group of cancer survivors with limited medical resources will be a key concern in the field of global public health in the future. Compared to developed countries, China's theoretical research and practical experience in care for cancer survivors are relatively limited and cannot meet the multi-faceted and diverse care needs of cancer patients. Based on the existing models of care worldwide, the current work reviews care for cancer survivors in China, it proposes considerations and suggestions for the creation of models of cancer care with Chinese characteristics in terms of optimizing top-level system design, enhancing institutional mechanisms, accelerating human resource development, and enhancing self-management and social support for patients.

***Keywords*:** cancer survivors, model of care, quality of life, survivorship, China

Introduction

Cancer is a major public health problem worldwide, with an estimated 19.3 million new cases and nearly 10 million deaths occurring in 2020. The current state of cancer prevention and control in China is dire, with a higher disease burden than in other countries. China is estimated to account for 23.7% of new cancer cases and 30.2% of deaths worldwide (*1*). With the development of cancer screening, treatment modalities, and rehabilitation care, cancer survival rates have gradually improved and the number of survivors has increased. The latest data from the American Centers Society (ACS) in 2023 show that overall cancer mortality in the US fell by 33% between 1991 and 2020, meaning that 3.82 million cancer survivors were saved from dying (*2*). The National Cancer Centre of China reports that overall cancer survival rates in China are all on the rise, with a 5-year survival rate of approximately 40.5% (*3,4*).

In China, the most common types of cancer were those of the lung (20.4%), colorectum (10.0%), stomach (9.8%), liver (9.6%), and breast (7.5%), accounting for 57.3% of all new cancer cases. Lung cancer (27.2%), liver cancer (13.9%), and gastric cancer (12.0%) were the three malignant tumors with the highest mortality rates in the general population (*5*). China is undergoing a transition in cancer where the cancer spectrum is changing from that of a developing country to that of a developed country (*6*). Highly prevalent cancers are generally characterized by long disease duration and complex treatments, which impose a heavy financial burden of illness on patients' families and society. In 2015, total payments for cancer inpatients reached 177.1 billion RMB, accounting for 4.3% of China's total health costs (*6*). Huang *et al.* reported the results of the economic burden of disease for cancer patients in China, where the cost of treatment for cancer patients exceeded annual household income (average annual household income: $8,607 *vs.* per capita expenditure on medical visits: $,9739); 9.3% of the non-direct medical costs were associated with the disease (*7*).

In addition to the financial burden, cancer survivors will face many potential long-term or late effects of oncological treatment, such as cardiac dysfunction, metabolic syndrome, and peripheral neuropathy that will severely impact their quality of life. At the same time, the negative effects of the illness such as fear of relapse, fatigue, impacts on sexual and intimate relationships, and impacts on work and social interaction require effective psychosocial care. Several studies have indicated that cancer survivors in China have significant unmet healthcare needs (*8,9*). Medical resources from medical facilities, oncologists, family doctors, and nurses are not efficiently integrated, and cancer survivors need guidance in self-management. There is a huge gap in the system of care covering the whole population and the whole life

cycle (*10*). Future models of improved care for cancer survivors are expected to focus on both "screening" and "rehabilitation", improving the quality of life, functional outcomes, well-being, and long-term survival of cancer survivors, reducing the risk of recurrence and incidence of new cancer, improving the management of comorbidities, and reducing costs to patients and payers.

Models of care for cancer survivors worldwide

The 2005 Institute of Medicine (IOM) and National Research Council (NRC) consensus study reported four essential components of survivorship care for cancer survivors: *i*) prevention of recurrent and new cancers, and other late effects; *ii*) surveillance for cancer spread and recurrence, and for medical and psychosocial effects; *iii*) intervention for consequences of cancer and its treatment (*e.g.*, medical problems such as lymphedema and sexual dysfunction; symptoms, including pain and fatigue; psychological distress experienced by cancer survivors and their caregivers; and concerns related to employment and insurance); and *iv*) coordination between specialists and primary care providers to ensure that all of the survivor's health needs are met (*e.g.*, health promotion, immunizations, screening for both cancer and noncancerous conditions, and the care of concurrent conditions) (*11,12*).

Concerns have been raised about the sustainability of the traditional oncologist-led model of care for cancer survivors, which includes medical oncologists, surgical oncologists, radiation oncologists, and hematologists (*13*). The increasing number of cancer survivors, the shortage of specialists, the cost constraints of healthcare, and the lack of professional nursing experience in primary care are all affecting the unmet needs of cancer survivors and challenging traditional models of medical care (*14*). To ensure efficient and continuous care for cancer survivors, a variety of models of care are also being actively explored in developed countries including general practitioner-led follow-up care models, shared care models, and oncology nurse-led care models (Table 1). Other complementary models include long-term follow-up clinics, self-support management, and integrated multidisciplinary rehabilitation (*10,15*). These new models encouraged non-oncology physician groups, multiple stakeholders in cancer care, and survivors themselves to join the system of care for cancer survivors (*16*). Improved models of care contribute to the development of "value-based care (VBC)" and promote efficient and collaborative models of cancer care (*17*).

Current state of care for cancer survivors in China

Cancer prevention and treatment is an important part of achieving "Healthy China". In 2019, the National Health Commission of China and other government agencies jointly published *the Notice on the Issuance of the Healthy China Initiative - A Plan to Implement Cancer Prevention and Treatment (2019-2022)*, which calls for comprehensive improvement of national cancer prevention and treatment in terms of controlling risk factors, enhancing prevention and treatment capabilities, improving the registration system, promoting early diagnosis and treatment, and increasing scientific and technological research (*18*).

Similar to the oncologist-led follow-up care model in developed countries, care for cancer survivors in China mainly relies on cancer treatment centers, oncologists, and their medical teams. The main providers of care for cancer survivors in China include tertiary hospitals (or specialist hospitals), secondary hospitals (or rehabilitation centers), community hospitals (or primary hospitals), and nursing facilities (*19*). Tertiary and secondary hospitals provide specialist care including cancer treatment, symptomatic treatment, and specialized care (*20*). Some community hospitals provide home follow-up for cancer survivors and use Chinese medicine to help patients relieve their discomfort (*21*). Nursing facilities provide palliative care and hospice care for terminal cancer survivors. At the same time, other forms of follow-up care are gradually being developed, such as promoting the use of online hospitals, mobile phones, and apps to better monitor and manage cancer survivors' side effects, physical activity levels, daily diet, mental health, *etc.* (*22*).

Medical consortia are a forward-looking approach to creating a hierarchical system of medical care in China, promoting the establishment of partnerships between hospitals at different levels to facilitate the optimal allocation of medical resources. Senior oncologists with experience in cancer treatment periodically assist primary care providers in teaching and training at secondary and community hospitals (*23*). An electronic patient health records system is being set up in China. For newly diagnosed cancer patients, the hospital will report the patient's information to the regional Centers for Disease Control and Prevention (CDC) through the Tumor Registry Card for statistical and dynamic health monitoring (*24*). The "discharge summary" provided by the hospital to the patient will help oncologists at different facilities to better understand the patient's medical history and provide continuity of care for the patient. Some hospitals that have joined the clinical information exchange platform can share and access some of the patient's information (*25*).

Outlook for care for cancer survivors in China

China's system of care for cancer survivors is being gradually improved. In general, cancer survivorship care in China still rely mainly on oncology physicians and their teams, while primary care physicians, nurses, rehabilitation teams, and other non-oncology physician groups play a very limited role in the care of cancer

Table 1. Models of care for cancer survivors and their characteristics

Model of care	Model type	Characteristics	Provider	Advantages	Suitable patients
Major models	Specialist-led care	● Based on oncologists and large cancer centers; ● Provides targeted treatment for patients in the acute phase of cancer and follow-up care for post-cancer survival.	Cancer specialists	● Highly specialized care; ● Provides continuous treatment and care.	● Patients at higher risk of recurrence/new cancer; ● Patients with complex cancer.
	General practitioner-led care	Patients receive survivorship care mainly or only in primary care facilities.	Primary care providers	● Easy access for patients; ● Primary care providers are more familiar with the patient's health status; ● Highly cost-effective.	● Patients with early-stage breast cancers/colorectal cancer/ prostate cancer/melanoma; ● Other cancer survivors with a low risk of recurrence and late effects of treatment.
	Shared care	Oncologists and general practitioners work in collaboration to provide specialized and continuous care for cancer patients.	Cancer specialists and general practitioners	● Highly specialized care; ● Provide continuous treatment and care; ● Higher patient satisfactory; ● Highly cost-effective.	Most cancer survivors.
	Oncology nurse-led care	Trained and qualified oncology nurses provide integrated care for cancer patients, including prevention, assessment, diagnosis, care, follow-up, and education.	Qualified oncology nurses	● Highly specialized care; ● Higher patient satisfaction; ● Highly cost-effective.	Cancer survivors with low/medium risk of recurrence and late effects of treatment.
Complementary models	Long-term follow-up clinics	Comprehensive long-term care for cancer survivors.	Multiple medical specialties	● Highly specialized care; ● Provides continuous treatment and care; ● Long-term follow-up.	● Survivors of childhood and adolescent cancer; ● Patients with rare cancer; ● Groups of cancer patients with complex treatment or severe late effects of treatment.
	Supported self-management	Development of cancer patients' competencies in symptom management, self-healing, and health behavior development.	Cancer survivors	● Timely recognition of and response to changes in disease; ● Encouraging healthy behaviors	Most cancer survivors.
	Comprehensive multidisciplinary rehabilitation	A rehabilitation team consisting of staff from different disciplines such as medicine, education, sociology, psychological counseling, and career planning comprehensively assesses and treats the physical and psychological damage to cancer patients due to the disease and the corresponding treatment.	Multidisciplinary rehabilitation team	● Full cycle of rehabilitation; ● Comprehensive rehabilitation.	Most cancer survivors.

survivors. Care for cancer survivors in China still faces many challenges, including the lack of clear goals and plans for care for cancer survivors at the national level, the overall uneven distribution of healthcare resources, the lack of guidelines and standards of care for cancer survivors, the shortage and varying abilities of care professionals, the serious fragmentation of cancer management, and the lack of continuity of care (*26*). An imperative task is to create a model of quality care for cancer survivors with Chinese characteristics (Figure 1).

Optimize the top-level system design

Improve the national cancer control plan

The current national cancer control plan mainly focuses on cancer prevention and treatment but lacks clear goals and plans to care for cancer survivors (*18*). The system of care for cancer survivors should be an important part of the national cancer control plan. The division of responsibilities among relevant facilities should be clarified to promote collaboration among relevant departments, facilities, and society as a whole.

Develop guidelines on care for cancer survivors

Given China's healthcare system and medical insurance, relevant societies and associations should, in concert with multidisciplinary teams of experts, comprehensively integrate and analyze literature and research with evidence-based ratings and fully consider the actual needs of patients and caregivers to jointly draft and formulate various guidelines on cancer care (*27*). For young cancer patients, relevant facilities should provide special guidelines on care to better protect the health-related rights of a vulnerable population (*28*). In addition, due to the uneven distribution of care resources in different provinces and cities, the national government can formulate guidelines on care with resource stratification depending to the supply of care resources and encourage regions to explore appropriate models of care in accordance with local conditions.

Enhancing institutional mechanisms

Develop a survivorship care plan (SCP)

There is still in a gap in the practice of SCPs in China. The formulation and implementation of an efficient SCP for cancer survivors is urgently needed to provide quality care in China. National standardization of SCPs should be promoted based on improvements in relevant guidelines. Steps that need to be taken are to identify for whom an SCP is being formulated, standardizing the formulation process, improving plan details, and incorporating the opinions of healthcare workers, patients, and care-related organizations to promote the formulation and implementation of SCPs in phases in light of conditions in China (*29*). To evaluate the effectiveness of SCPs, a short-term goal that can be focused on is increasing patients and healthcare workers' awareness of the disease and survival care, and a long-term goal can be to further examine how SCPs affect patients' health outcomes (*30,31*).

Implement risk stratification

At present, the external conditions have been created for the implementation of risk stratification for cancer patients in China: a multi-level system of medical insurance has been created, insurers have developed strategic purchasing power, the creation of medical consortia has been extensively advanced, hierarchical models of diagnosis and treatment are being created, and the capacity of community hospitals has been continuously improved. Clinical experts and academic

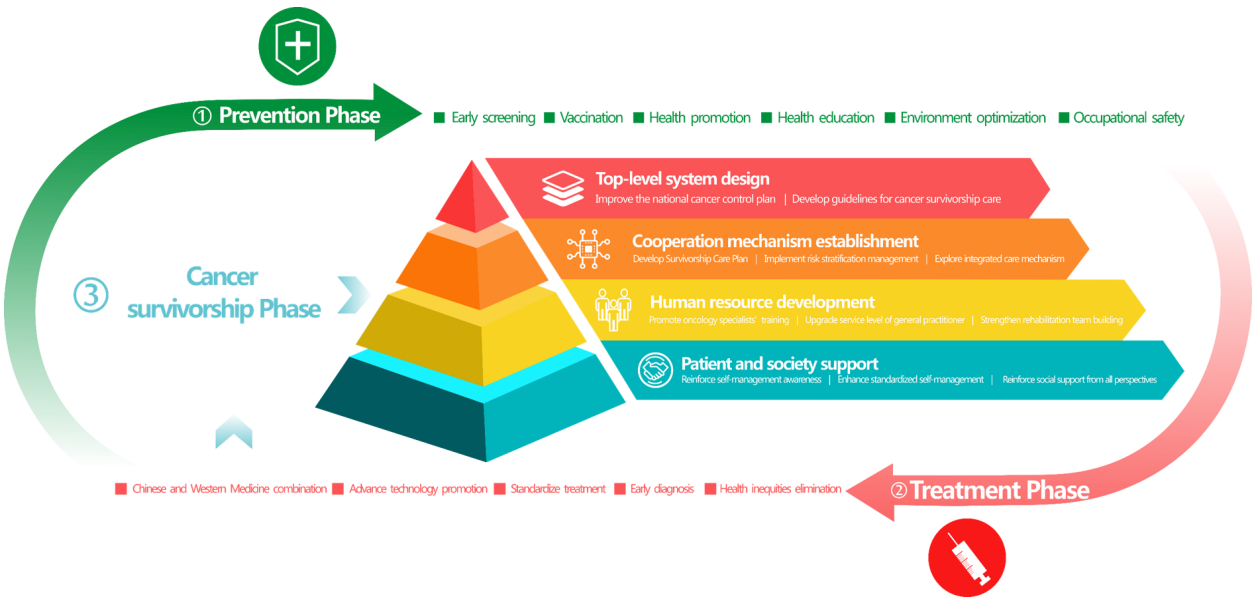


Figure 1. A model of quality care for cancer survivors with Chinese characteristics.

scholars should work with relevant societies and associations to formulate and implement guidelines and norms for cancer survival risk stratification. Pilot risk stratification should be promoted in limited areas, its effects should be timely ascertained and evaluated, and the pilot project's scope should be expanded when appropriate (*32,33*). For developed regions, some care can be included in social/medical insurance, and the reimbursement rate for different levels of facilities can be increased to encourage low-risk patients to follow-up at primary medical and rehabilitation facilities to optimize the allocation of medical and healthcare resources (*26*). The complementary role of commercial insurance in rehabilitation and health management should be gradually improved.

Exploring mechanisms of integrated care

At present, the capacity of primary healthcare facilities in China is steadily improving. The hierarchical model of diagnosis and treatment is evolving. The time is ripe to explore mechanisms of integrated care for cancer patients (*34*). To accelerate the creation of an integrated care system for cancer patients, the following aspects could be considered: *i*) Create consortia for integrated cancer care: Based on existing medical consortia, rehabilitation facilities, nursing homes, hospices, and other related facilities should be included into the consortium, coordination and communication within and among the consortium facilities should be enhanced, triage and referral should be improved, and an integrated cancer treatment and care consortium should be gradually created (*35*). *ii*) Explore navigation program for cancer patients: Both healthcare professionals and non-professionals can be recruited as patient navigators. They should provide coordinated, integrated, and continuous navigation to patients by enhancing communication, identifying patient needs, coordinating among institutions, and providing health education (*36*). *iii*) Make substantial efforts to encourage the development of information technology: Online healthcare platforms should be continuously improved and cancer patients should be provided convenient care such as remote treatment, disease monitoring, and health education through the use advanced information technology so that different facilities can efficiently communicate and collaborate (*37*). *iv*) Establish a mechanism of tracking and evaluation: To improve the patient experience and clinical results, the outcomes of integrated care need to be tracked and evaluated, and mechanisms for tracking and evaluation should be modified and optimized in a timely manner (*38*).

Accelerate human resource development

Promote training for oncology specialists

In terms of training for oncology specialists, the threshold for admission to oncology-related disciplines can be raised to an appropriate extent to focus more resources on quality students. Strengthen oncology specialty training for students at school and during standardized training. Homogenization of oncology discipline education should be enhanced (*39*). To foster quality oncology specialists, problem-based learning (PBL), case-based learning (CBL), and multi-disciplinary teams (MDTs) should be combined to create a comprehensive training and evaluation system that includes theoretical foundations, clinical skills, medical ethics, medical regulations, evidence-based medicine, *etc.* (*40*). Relevant authorities and corresponding social organizations should gradually clarify the standards of practice for oncology nurses, create and improve the certification system, and comprehensively standardize the training process. Efforts should also be made to enhance the training of oncology nurses in disease prevention and treatment, patient communication and education, and clinical management and research; the professional development of nurses should be promoted to foster specialists in clinical nursing (*41,42*).

Improve the level of care by general practitioners in the community

General medical education should be considered an important part of medical education, and it should be included in the early training of medical students. The core competency of general practitioners should be comprehensively improved. A system should also be created to train general practitioners in oncology-related expertise, and certification should be strictly controlled and dynamically monitored (*43,44*). Communication between general practitioners and patients should be continuously enhanced so that patients will gain more trust in their healthcare providers. Efforts should also be made to facilitate efficient collaboration within the general practitioner-led care team so that multidisciplinary team members with a clear division of responsibilities provide quality and continuous care to survivors. In addition, cooperation between regions at different levels of development should be enhanced to eliminate health inequalities and to help improve general medical care in rural and remote areas (*45,46*).

Strengthen rehabilitation teams

First, the concept of "full-cycle, whole family, whole person rehabilitation" should be integrated into all aspects of rehabilitation training. Pre-habilitation should also be emphasized so that rehabilitation for cancer survivors covers all stages of the disease, from diagnosis to survivorship. Patient-centered rehabilitation should also be encouraged by involving patients in the design and optimization of cancer rehabilitation programs (*47*). Second, advances should be promoted in rehabilitation medicine and the training of highly specialized rehabilitation personnel (including rehabilitation physicians, physical therapists, occupational

therapists, speech therapists, swallowing therapists, psychotherapists, nutritionists, *etc.*) should be accelerated (*48,49*). Third, a cooperative teamwork model should be created around rehabilitation physicians working closely with multidisciplinary personnel. The standardized and orderly progression of cancer rehabilitation should be promoted.

Enhance patient self-management and social support

Cancer survivors should be taught that they are the gatekeepers of their own health. They should pay more attention to their physical and mental health and promptly identify circumstances that may indicate recurrent and new cancers (*50*). They should also actively improve their health literacy regarding cancer and strive to motivate themselves to appropriately modify their emotions, behavior, and circumstances (*51*). Second, standardized self-management for cancer survivors should be enhanced, which should be incorporated into guidelines on routine survivorship care and survival care plans. Patient self-management capabilities should be assessed in detail and should be incorporated in stages step by step; these capabilities can be capitalized on in different models of care and care scenarios (*52*). The standardization of self-management should be improved through patient education, standardized training, and the development of mobile applications (*53*). Research on the effectiveness of self-management by cancer patients should be increased, the effectiveness of self-management should be comprehensively evaluated from multiple perspectives such as clinical outcomes, alleviation of symptoms, and patient experience, and self-management models should be continuously adjusted and optimized for different types of cancer, risk factors, and population characteristics (*54*). In addition, comprehensive support for cancer patients should be enhanced at the societal level, including provision of information, emotional support, and financial support. On the one hand, friends and relatives of survivors should be encouraged to be more patient and inclusive, discrimination in the workplace should be eliminated, and social care and concern for cancer patients should be increased (*55,56*). On the other hand, patients should be encouraged to share positive experiences fighting cancer with other patients, scientific knowledge of cancer prevention should be promoted, and patients should be encouraged to value their own self-worth (*57,58*).

Conclusion

The "Healthy China 2030" plan intends for chronic disease management for the whole population and the whole life cycle to be achieved by 2030 and for the overall 5-year survival rate from cancer to increase by 15%. At present, China has made great achievements in spreading early diagnosis and treatment, establishing a long-term mechanism for screening, standardizing and improving diagnosis and treatment capacity, and steadily improving medical insurance. With cancer treatment entering the era of chronic disease management, accelerating the creation of a model of care for cancer survivors with Chinese characteristics can further improve the patient survival rate, enhance their quality of life, rationally allocate medical resources, and efficiently utilize medical insurance, helping to create a healthy China.

Funding: This study was supported by grants from the China Medical Board for "The study of a home-based supportive care system for cancer patients receiving oral chemotherapy" (No. 20-387) and the Shanghai Municipal Health Commission for "Exploration of chronic disease management model for cancer patients in the post-epidemic era" (No. 202240061).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021; 71:209-249.
2. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023; 73:17-48.
3. Zeng H, Chen W, Zheng R, *et al*. Changing cancer survival in China during 2003-15: A pooled analysis of 17 population-based cancer registries. Lancet Glob Health. 2018; 6:e555-e567.
4. Zheng R, Zhang S, Zeng H, Wang S, Sun K, Chen R, Li L , Wei W, He J. Cancer incidence and mortality in China, 2016. J Natl Cancer Center. 2022; 2:1-9.
5. Cao M, Li H, Sun D, He S, Yang X, Yang F, Zhang S, Xia C, Lei L, Peng J, Chen W. Current cancer burden in China: Epidemiology, etiology, and prevention. Cancer Biol Med. 2022; 19:1121-1138.
6. Feng RM, Zong YN, Cao SM, Xu RH. Current cancer situation in China: Good or bad news from the 2018 Global Cancer Statistics? Cancer Commun (Lond). 2019; 39:22.
7. Huang HY, Shi JF, Guo LW, *et al*. Expenditure and financial burden for the diagnosis and treatment of colorectal cancer in China: A hospital-based, multicenter, cross-sectional survey. Chin J Cancer. 2017; 36:41.
8. Bu X, Jin C, Fan R, Cheng ASK, Ng PHF, Xia Y, Liu X. Unmet needs of 1210 Chinese breast cancer survivors and associated factors: A multicentre cross-sectional study. BMC Cancer. 2022; 22:135.
9. Chen M, Li R, Chen Y, Ding G, Song J, Hu X, Jin C. Unmet supportive care needs and associated factors: Evidence from 4195 cancer survivors in Shanghai, China. Front Oncol. 2022; 12:1054885.
10. Jefford M, Howell D, Li Q, Lisy K, Maher J, Alfano CM, Rynderman M, Emery J. Improved models of care for cancer survivors. Lancet. 2022; 399:1551-1560.

11. National Research Council, Institute of Medicine, National Cancer Policy Board, *et al*. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, D.C.: National Academies Press; 2005.
12. National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Health Care Services; National Cancer Policy Forum. Long-term survivorship care after cancer treatment: Proceedings of a workshop. Washington (DC): National Academies Press (US); 2018.
13. Dossett LA, Hudson JN, Morris AM, Lee MC, Roetzheim RG, Fetters MD, Quinn GP. The primary care provider (PCP)-cancer specialist relationship: A systematic review and mixed-methods meta-synthesis. CA Cancer J Clin. 2017; 67:156-169.
14. Neuman HB, Jacobs EA, Steffens NM, Jacobson N, Tevaarwerk A, Wilke LG, Tucholka J, Greenberg CC. Oncologists' perceived barriers to an expanded role for primary care in breast cancer survivorship care. Cancer Med. 2016; 5:2198-2204.
15. Vaz-Luis I, Masiero M, Cavaletti G, *et al.* ESMO Expert Consensus Statements on Cancer Survivorship: Promoting high-quality survivorship care and research in Europe. Ann Oncol. 2022; 33:1119-1133.
16. Halpern MT, Cohen J, Lines LM, Mollica MA, Kent EE. Associations between shared care and patient experiences among older cancer survivors. J Cancer Surviv. 2021; 15:333-343.
17. Teisberg E, Wallace S, O'Hara S. Defining and implementing value-based health care: A strategic framework. Acad Med. 2020; 95:682-685.
18. National Health Commission of China. Notice on the issuance of the Healthy China Initiative - A Plan to Implement Cancer Prevention and Treatment (2019-2022). *http://www.gov.cn/zhengce/zhengceku/2019-11/13/content_5451694.htm* (Accessed February 8, 2023). (in Chinese)
19. Liu Y, Kong Q, Yuan S, van de Klundert J. Factors influencing choice of health system access level in China: A systematic review. PLoS One. 2018; 13:e0201887.
20. Liu Y, Zhong L, Yuan S, van de Klundert J. Why patients prefer high-level healthcare facilities: A qualitative study using focus groups in rural and urban China. BMJ Glob Health. 2018; 3:e000854.
21. Zhang X, Qiu H, Li C, Cai P, Qi F. The positive role of traditional Chinese medicine as an adjunctive therapy for cancer. Biosci Trends. 2021; 15:283-298.
22. Wang Y, Liu Y, Shi Y, Yu Y, Yang J. User perceptions of virtual hospital apps in China: Systematic search. JMIR Mhealth Uhealth. 2020; 8:e19487.
23. Gao H, Du XL, Liao JZ, Xiang L. The pathway of China's integrated delivery system: Based on the analysis of the medical consortium policies. Curr Med Sci. 2022; 42:1164-1171.
24. Wei W, Zeng H, Zheng R, Zhang S, An L, Chen R, Wang S, Sun K, Matsuda T, Bray F, He J. Cancer registration in China and its role in cancer prevention and control. Lancet Oncol. 2020; 21:e342-e349.
25. Tang W. The creation of a continuum of care model for cancer patients in Shanghai. Second Military Medical University; Shanghai, China, 2011. (in Chinese)
26. Chen R, Yang J, Yin S, Chen W, Liu Y. International models of care for cancer survivors: Recent advances and implications in China. Chinese General Medicine. 2022; 25:401-407. (in Chinese)
27. van Kalsbeek RJ, van der Pal HJH, Kremer LCM, *et al.* European PanCareFollowUp Recommendations for surveillance of late effects of childhood, adolescent, and young adult cancer. Eur J Cancer. 2021; 154:316-328.
28. Sender L, Zabokrtsky KB. Adolescent and young adult patients with cancer: A milieu of unique features. Nat Rev Clin Oncol. 2015; 12:465-480.
29. Hill RE, Wakefield CE, Cohn RJ, Fardell JE, Brierley ME, Kothe E, Jacobsen PB, Hetherington K, Mercieca-Bebber R. Survivorship care plans in cancer: A meta-analysis and systematic review of care plan outcomes. *Oncologist.* 2020; 25:e351-e372.
30. Jacobsen PB, DeRosa AP, Henderson TO, Mayer DK, Moskowitz CS, Paskett ED, Rowland JH. Systematic review of the impact of cancer survivorship care plans on health outcomes and health care delivery. J Clin Oncol. 2018; 36:2088-2100.
31. Ma CT, Chou HW, Lam TT, Tung YT, Lai YW, Lee LK, Lee VW, Yeung NC, Leung AW, Bhatia S, Li CK, Cheung YT. Provision of a personalized survivorship care plan and its impact on cancer-related health literacy among childhood cancer survivors in Hong Kong. Pediatr Blood Cancer. 2023; 70:e30084.
32. Mayer DK, Alfano CM. Personalized risk-stratified cancer follow-up care: Its potential for healthier survivors, happier clinicians, and lower costs. J Natl Cancer Inst. 2019; 111:442-448.
33. Tremblay D, Touati N, Bilodeau K, Prady C, Usher S, Leblanc Y. Risk-stratified pathways for cancer survivorship care: Insights from a deliberative multi-stakeholder consultation. Curr Oncol. 2021; 28:3408-3419.
34. Mukumbang FC, De Souza D, Liu H, Uribe G, Moore C, Fotheringham P, Eastwood JG. Unpacking the design, implementation and uptake of community-integrated health care services: A critical realist synthesis. BMJ Glob Health. 2022; 7:e009129.
35. Qian Y, Hou Z, Wang W, Zhang D, Yan F. Integrated care reform in urban China: A qualitative study on design, supporting environment and implementation. Int J Equity Health. 2017; 16:185.
36. Ramirez AG, Choi BY, Munoz E, Perez A, Gallion KJ, Moreno PI, Penedo FJ. Assessing the effect of patient navigator assistance for psychosocial support services on health-related quality of life in a randomized clinical trial in Latino breast, prostate, and colorectal cancer survivors. Cancer. 2020; 126:1112-1123.
37. Bevilacqua R, Strano S, Di Rosa M, Giammarchi C, Cerna KK, Mueller C, Maranesi E. eHealth literacy: From theory to clinical application for digital health improvement. Results from the ACCESS training experience. Int J Environ Res Public Health. 2021; 18:11800.
38. Ramanuj P, Ferenchik E, Docherty M, Spaeth-Rublee B, Pincus HA. Evolving models of integrated behavioral health and primary care. Curr Psychiatry Rep. 2019; 21:4.
39. Ye C, Mi M, Zheng S, Yuan Y. Implications of medical education in the United States for the training of oncology specialists in China. General Medicine Clinical and Education. 2022; 20:385-387. (in Chinese)
40. Yu H, Li L, Xu J. Use of MDT and PBL-CBL in the clinical teaching of lymphoma. Basic and Clinical Oncology. 2019; 32:269-271. (in Chinese)
41. Bryant-Lukosius D, Spichiger E, Martin J, Stoll H, Kellerhals SD, Fliedner M, Grossmann F, Henry M, Herrmann L, Koller A, Schwendimann R, Ulrich

A, Weibel L, Callens B, De Geest S. Framework for evaluating the impact of advanced practice nursing roles. J Nurs Scholarsh. 2016; 48:201-209.
42. Kerr H, Donovan M, McSorley O. Evaluation of the role of the clinical Nurse Specialist in cancer care: an integrative literature review. Eur J Cancer Care (Engl). 2021; 30:e13415.
43. Rao X, Lai J, Wu H, Li Y, Xu X, Browning CJ, Thomas SA. The development of a competency assessment standard for general practitioners in China. Front Public Health. 2020; 8:23.
44. Shi J, Du Q, Gong X, Chi C, Huang J, Yu W, Liu R, Chen C, Luo L, Yu D, Jin H, Yang Y, Chen N, Liu Q, Wang Z. Is training policy for general practitioners in China charting the right path forward? A mixed methods analysis. BMJ Open. 2020; 10:e038173.
45. Tam YH, Leung JYY, Ni MY, Ip DKM, Leung GM. Training sufficient and adequate general practitioners for universal health coverage in China. BMJ. 2018; 362:k3128.
46. Li X, Krumholz HM, Yip W, *et al.* Quality of primary health care in China: Challenges and recommendations. Lancet. 2020; 395:1802-1812.
47. Santa Mina D, van Rooijen SJ, Minnella EM, *et al.* Multiphasic prehabilitation across the cancer continuum: A narrative review and conceptual framework. Front Oncol. 2020; 10:598425.
48. Kudre D, Chen Z, Richard A, Cabaset S, Dehler A, Schmid M, Rohrmann S. Multidisciplinary outpatient cancer rehabilitation can improve cancer patients' physical and psychosocial status-A systematic review. Curr Oncol Rep. 2020; 22:122.
49. Gong J, Li G, Jiang Y, Ye L. Thinking and practice on the training of rehabilitation therapy talents under the concept of "precision medicine". China Continuing Medical Education. 2022; 14:13-16. (in Chinese)
50. Agbejule OA, Hart NH, Ekberg S, Crichton M, Chan RJ. Self-management support for cancer-related fatigue: A systematic review. Int J Nurs Stud. 2022; 129:104206.
51. Boland L, Bennett K, Connolly D. Self-management interventions for cancer survivors: A systematic review. Support Care Cancer. 2018; 26:1585-1595.
52. Dunne S, Coffey L, Sharp L, Desmond D, Gooberman-Hill R, O'Sullivan E, Timmons A, Keogh I, Timon C, Gallagher P. Integrating self-management into daily life following primary treatment: Head and neck cancer survivors' perspectives. J Cancer Surviv. 2019; 13:43-55.
53. Schmidt F, Ribi K, Haslbeck J, Urech C, Holm K, Eicher M. Adapting a peer-led self-management program for breast cancer survivors in Switzerland using a co-creative approach. Patient Educ Couns. 2020; 103:1780-1789.
54. Clarke N, Dunne S, Coffey L, Sharp L, Desmond D, O'Conner J, O'Sullivan E, Timon C, Cullen C, Gallagher P. Health literacy impacts self-management, quality of life and fear of recurrence in head and neck cancer survivors. J Cancer Surviv. 2021; 15:855-865.
55. Coffey L, Mooney O, Dunne S, Sharp L, Timmons A, Desmond D, O'Sullivan E, Timon C, Gooberman-Hill R, Gallagher P. Cancer survivors' perspectives on adjustment-focused self-management interventions: A qualitative meta-synthesis. J Cancer Surviv. 2016; 10:1012-1034.
56. Campanini I, Ligabue MB, Bò MC, Bassi MC, Lusuardi M, Merlo A. Self-managed physical activity in cancer survivors for the management of cancer-related fatigue: A scoping review. PLoS One. 2022; 17:e0279375.
57. Zhang S, Li J, Hu X. Peer support interventions on quality of life, depression, anxiety, and self-efficacy among patients with cancer: A systematic review and meta-analysis. Patient Educ Couns. 2022; 105:3213-3224.
58. Yoshikawa E, Fujisawa D, Hisamura K, Murakami Y, Okuyama T, Yoshiuchi K. The potential role of peer support interventions in treating depressive symptoms in cancer patients. J Nippon Med Sch. 2022; 89:16-23.

Received March 7, 2023; Revised May 1, 2023; Accepted May 9, 2023.

Released online in J-STAGE as advance publication May 12, 2023.

[§]*These authors contributed equally to this work.*
**Address correspondence to*:
Minxing Chen and Chunlin Jin, Shanghai Health Development Research Center, Shanghai Medical Information Center, Jianguo (W) Road No.602, Xuhui District, Shanghai 200031, China.
E-mail: chenminxing@shdrc.org (MC); jinchunlin@shdrc.org (CJ)

Global Health & Medicine. 2023; 5(4):216-222.
ORIGINAL ARTICLE
DOI: 10.35772/ghm.2023.01060

Steady-state pharmacokinetics of plasma tenofovir alafenamide (TAF), tenofovir (TFV) and emtricitabine (FTC), and intracellular TFV-diphosphate and FTC-triphosphate in HIV-1 infected old Japanese patients treated with bictegravir/FTC/TAF

Hieu Trung Tran[1,2,3,*], Kiyoto Tsuchiya[1], Akira Kawashima[1,2], Koji Watanabe[1], Yoshiharu Hayashi[4], Shoraku Ryu[4], Akinobu Hamada[4], Hiroyuki Gatanaga[1,2], Shinichi Oka[1,2]

[1] AIDS Clinical Center, National Center for Global Health and Medicine, Tokyo, Japan;
[2] The Joint Research Center for Human Retrovirus Infection, Kumamoto University, Kumamoto, Japan;
[3] Hanoi Medical University, Hanoi, Vietnam;
[4] Division of Molecular Pharmacology, National Cancer Center Research Institute, Tokyo, Japan.

Abstract: Emtricitabine (FTC) plus tenofovir alafenamide (TAF) has demonstrated efficacy and safety for pre-exposure prophylaxis (PrEP) to prevent HIV-1 infection. We measured the plasma PK of FTC, tenofovir (TFV), and TAF in a steady-state pharmacokinetic (PK) study of bictegravir/FTC/TAF in HIV-1-infected patients. Furthermore, validated liquid chromatography-tandem mass spectrometry was used to measure intracellular TFV-diphosphate (DP) and FTC-triphosphate (TP), the active metabolites of TFV and FTC, respectively. Plasma and dried blood spot samples were collected from 10 male patients aged ≥ 50 years at various time intervals: 0 (trough), 1, 2, 3, 4, 6, 8, 12, and 24 h after drug administration. The mean ± standard deviation of plasma PK parameters were as follows: The maximum concentrations of TAF, TFV, and FTC were 104.0 ± 72.5, 27.9 ± 5.2, and 3,976.0 ± 683.6 ng/mL, respectively. Additionally, their terminal elimination half-lives were 0.6 ± 0.5, 31.6 ± 10.4, and 6.9 ± 1.4 h, respectively. These results were consistent with previously reported data. The intracellular levels of TFV-DP and FTC-TP varied widely among individuals; however, they remained stable over 24 h in each individual at approximately 1,000–1,500 and 2,000–3,000 fmol/punch, respectively, indicating that plasma concentrations did not affect the intracellular concentrations of their active metabolites. These results demonstrated that measuring intracellular TFV-DP and FTC-TP could be useful for monitoring adherence to PrEP in clients on this regimen.

Keywords: pre-exposure prophylaxis, plasma concentration, intracellular concentration, liquid chromatography-tandem mass spectrometry, dried blood spot

Introduction

Bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) is well known as an effective and well-tolerated regimen for the initial treatment of HIV-1 infection in adults (*1*). This medication consists of an integrase strand transfer inhibitor (INSTI) of BIC and two nucleoside reverse transcriptase inhibitors (NRTIs), FTC and TAF (*2*). However, the pharmacokinetic (PK) data for the elderly Japanese population are currently limited. Here, we conducted a prospective steady-state PK study of BIC/FTC/TAF in elderly Japanese patients using previously published BIC data (*3*). In this study, we examined the remaining PK data for plasma FTC, TAF, and tenofovir (TFV), an intermediate metabolite of TAF. In addition, we examined the intracellular concentrations of FTC-triphosphate (TP) and TFV-diphosphate (DP), the active metabolites of FTC and TFV, respectively.

To prevent new cases of HIV infections, recent guidelines recommend using oral tenofovir disoproxil fumarate (TDF) or TAF and FTC as pre-exposure prophylaxis (PrEP) for men who have sex with men (MSM) to effectively reduce the likelihood of acquiring HIV, using either daily or event-controlled regimens (*4-7*). Since the viral load is used as an objective indicator to evaluate HIV treatment, the lack of a load that can be used in daily practice for PrEP makes it difficult to monitor adherence accurately. Non-pharmacological methods such as self-reporting, pill counts, and refill records have been used as alternative measures to determine adherence to PrEP (*8,9*). Recently, several pharmacological methods have been developed

to measure drug concentrations. TFV and FTC concentrations in the plasma, urine, and saliva have been used as objective indicators of adherence. Urine, saliva, and plasma samples are easily collected and can be used to confirm recent drug intake. However, given the short half-lives of these samples, drug concentrations must be examined soon after the drug administration, even though PrEP typically requires drugs to be administered in the evening. Urine and saliva concentrations vary significantly (*10-13*). Intracellular TFV-DP in peripheral blood mononuclear cells (PBMCs), the active ingredient in both TDFs and TAFs, is the most appropriate choice for assessing efficacy. Although TFV-DP has persistently high concentrations in PBMCs, the processing of PBMCs is time-consuming and requires accurate cell counts; therefore, it is not feasible on a large scale (*14*). To address these limitations, TFV-DP has been developed and validated in red blood cells (RBCs) using dried blood spots (DBS) and is being used as an adherence biomarker in several laboratories (*15-17*). However, methods for the measurement of intracellular TFV-DP and FTC-TP using DBS have not yet been established in Japanese participants.

In this study, we first examined the PK data of FTC, TAF, and TFV in plasma obtained from a prospective steady-state PK study of BIC/FTC/TAF in elderly HIV-1-infected Japanese patients (*3*). Furthermore, we prepared samples of DBS at the same time points as the plasma samples and developed a method to accurately measure the concentrations of intracellular TFV-DP and FTC-TP in DBS. We subsequently investigated the most appropriate markers for monitoring adherence to PrEP.

Materials and Methods

Subjects

This prospective cohort study was conducted at AIDS Clinical Center of National Center for Global Health and Medicine. Male HIV-1-infected Japanese patients with suppressed HIV RNA levels and without BIC-containing antiretroviral regimens were recruited (Supplemental files, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=67*). Peripheral blood samples were collected from each participant using heparin tubes for plasma and DBS analyses at multiple time points: 0 (trough), 1, 2, 3, 4, 6, 8, 12, and 24 h after drug administration (*3*). This research was conducted in compliance with the Declaration of Helsinki and national and institutional standards. The Institutional Review Board for Clinical Research of National Centre for Global Health and Medicine approved the study protocol (approval no. NCGM-G-003461-00), and all participants provided written informed consent prior to enrollment. The study protocol was registered at UMIN-CTR (UMIN00004113).

Measurement of plasma tenofovir alafenamide, tenofovir, and emtricitabine concentrations

TAF, TFV, FTC, TAF-d5 (internal standard [IS] of TAF), TFV-d6 (IS of TFV), and FTC-^{13}C,$^{15}N_2$ (IS of FTC) were purchased from Toronto Research Chemicals (Toronto, ON, Canada). Blank human plasma samples were purchased from Cosmo Bio (Tokyo, Japan). Plasma samples (100 μL) were deproteinized with ethanol. An ACQUITY UPLC H-Class system (Waters, Milford, MA, USA) and QTRAP 6500 mass spectrometer (AB Sciex, Framingham, MA, USA) equipped with an electrospray ionization source were used to measure the plasma concentrations of TAF, TFV, and FTC. Chromatographic separation was achieved on an ACQUITY UPLC HSS T3 column (50 × 2.1 mm, particle size 1.8 μm, Waters) using gradient elution with mobile phases A (20 mmol/L ammonium acetate containing 0.1% formic acid) and B (20 mmol/L ammonium acetate containing 0.1% formic acid in methanol/water (9:1, v/v)) at a flow rate of 0.4 mL/min. The gradient method consisted of the percentage change in mobile phase B in relation to time (0–0.5 min: 5% B; 0.5–2.7 min: 5 to 25% B; 2.7–4.5 min: 25 to 75% B; 4.5–6.0 min: 75 to 100% B; 6.0–|7.0: 100% B; 7.0–10.0 min: 100 to 5% B). The injection volume was 5 μL, and the run time was 10 min. The mass spectrometer was operated in the positive electrospray ionization mode. The mass transitions were m/z 477.3→364.1 for TAF and m/z 482.3→369.1 for TAF-d5, m/z 288.1→176.2 for TFV and m/z 294.1→182.2 for TFV-d6, and m/z 248.2→130.1 for FTC and m/z 251.2→133.1 for FTC-^{13}C,$^{15}N_2$. The calibration curves for TAF, TFV, and FTC were linear within the range of 0.5–500 ng/mL (r2 = 0.99). The intra- and inter-day precision and accuracy of TAF, TFV, and FTC in plasma had a coefficient of variation (CV) of 15.0%. The PK parameters were determined by non-compartmental analysis using the Phoenix WinNonlin version 8.2 software (Certara, Princeton, NJ, USA).

Measurement of intracellular tenofovir diphosphate and emtricitabine triphosphate concentrations

TFV-DP (tetra-ammonium salt) and FTC-TP (tetra-ammonium salt) were purchased from Toronto Research Chemicals. Meanwhile, $^{13}C_5$-TFV-DP (the IS of TFV-DP and FTC-TP) was purchased from Moravek Biochemicals (Brea, CA, USA).

We extracted a total of five punches (3 mm each) from the Whatman Protein Saver card of each patient in a microcentrifuge tube with 25 μL of methanol/water (1:1, v/v) and 400 μL of IS solution. Subsequently, 400 μL of supernatant from each tube was purified *via* a Solid Phase Extraction 96-well plate (Waters). A Shimadzu liquid chromatography system coupled with an 8050 triple quadrupole mass spectrometer (Kyoto, Japan) was then used to measure intracellular concentrations of the

analytes of interest. Analyte separation was achieved on an Atlantis Premier BEH C18 AX Column (50 × 2.1 mm, particle size 1.7 μm, Waters) at 40 °C with a 5.5-min gradient setting and 0.6 mL/min flow rate, using mobile phase A: 0.2% acetic acid/ methanol (1:4, v/v) and mobile phase B: (1M ammonia solution/1M ammonium acetate/water = 1:0.01:200, v/v)/methanol (9:1, v/v).

The gradient method consisted of the percentage change in mobile phase B over time (0–0.5 min: 0% B; 0.5–2.0 min: 0 to 95% B; 2.0–4.0 min: 95 to 100% B; 4.0–5.0 min: 100 to 0% B; 5.0–5.5 min: 0% B). The injection volume was 7 μL, and the run time was 5.5 min per sample. A mass spectrometer was used in positive electrospray ionization mode to detect the following analytes: m/z 448→176 for TFV-DP, m/z 488→130 for FTC-TP, and m/z 453→275 for $^{13}C_5$-TFV-DP. The quantifiable linear range for TFV-DP was 279–27901 fmol/punches ($r^2 = 0.99$), and that for FTC-TP was 256–25614 fmol/punches ($r^2 = 0.99$). The intra- and inter-day precision and accuracy of TFV-DP and FTC-TP were both within 15.0%.

Statistical analysis

Plasma PK parameters are expressed as mean ± standard deviation (SD). Plasma concentrations of TAF, TFV, and FTC and intracellular TFV-DP and FTC-TP at each time point are presented as the median ± interquartile range. Simple linear regression was used with *p* values < 0.05, indicating the presence of a statistically significant difference. All statistical analyses were performed using SPSS Statistics software version 23 (IBM, Armonk, NY, USA).

Results

Plasma concentrations of TAF, TFV, and FTC

Plasma samples were collected from the ten enrolled participants at the nine aforementioned time points before being measured (Table 1 and Figure 1). The maximum concentrations (C_{max}, mean ± SD) of TAF, TFV, and FTC were 104.0 ± 72.5 ng/mL (at 1.0 ± 0.0 h after dosing), 27.9 ± 5.2 ng/mL (at 2.2 ± 2.1 h after dosing), and 3,976. 0 ± 683.6 ng/mL (at 1.3 ± 0.7 h after dosing), respectively. The trough concentrations (C_{trough}, mean ± SD) of TAF and TFV were less than 0.5 ng/mL and 15.8 ± 3.0 ng/mL, respectively, whereas for FTC they varied within the range of 181.8 ± 49.7 ng/mL. The areas under the concentration-time curves for the last 24-h dosing intervals ($AUC_{0–24}$, mean ± SD) of TAF, TFV, and FTC were 127.9 ± 82.6 h*mg/mL, 484. 8 ± 79.4 h*mg/mL, and 22,417.1 ± 6,168.4 h*mg/mL, respectively. Furthermore, the elimination terminal half-lives ($T_{1/2}$, mean ± SD) of TAF and FTC were 0.6 ± 0.5 h and 6.9 ± 1.4 h, respectively. It should be noted that $T_{1/2}$ of TFV was 31.6 ± 10.4 h, or it could be expressed as stable.

Intracellular concentrations of TFV-DP and FTC-TP in DBS

The intracellular concentrations of TFV-DP and TFV-TP varied widely among the 10 patients while remaining stable in each individual patient. The median ± interquartile ranges at each time point of 0, 1, 2, 3, 4, 6, 8, 12, and 24 h are summarized in Table 2. In summary, the intracellular concentrations were approximately 1,000–1,500 fmol/punch for TFV-DP and 2,000–3,000 fmol/punches for FTC-TP over 24 h (Figure 2).

Correlation between plasma and intracellular concentration

There was no correlation between the plasma and intracellular concentrations of the following pairs: TAF and TFV-DP, TFV and TFV-DP, and FTC and FTC-TP. This strongly indicated that plasma concentrations did not affect the intracellular active metabolites (Figure 3).

Discussion

We examined the PK parameters of TAF, TFV, and FTC in plasma and intracellular TFV-DP and FTC-TP in DBS at nine time points in elderly HIV-1-infected Japanese patients to determine the markers that were the most valuable objective indicators for monitoring adherence to PrEP with FTC/TAF.

Our method showed that all results were well within the acceptance criteria for method validation. Several assays have been previously developed to detect the intracellular concentrations of TFV-DP and FTC-

Table 1. Pharmacokinetic parameters of tenofovir alafenamide, tenofovir, and emtricitabine in plasma

Items	Tenofovir alafenamide (mean ± SD)	Tenofovir (mean ± SD)	Emtricitabine (mean ± SD)
C_{max} (ng/mL)	104.0 ± 72.5	27.9 ± 5.2	3,976.0 ± 683.6
T_{max} (h)	1.0 ± 0.0	2.2 ± 2.1	1.3 ± 0.7
C_{trough} (ng/mL)	< 0.5	15.8 ± 3.0	181.8 ± 49.7
AUC_{0-24} (h*ng/mL)	127.9 ± 82.6	484.8 ± 79.4	22,417.1 ± 6,168.4
$T_{1/2}$ (h)	0.6 ± 0.5	31.6 ± 10.4	6.9 ± 1.4

C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; C_{trough}, trough plasma concentration; AUC, area under the plasma concentration-time curve; $T_{1/2}$, elimination half-life.

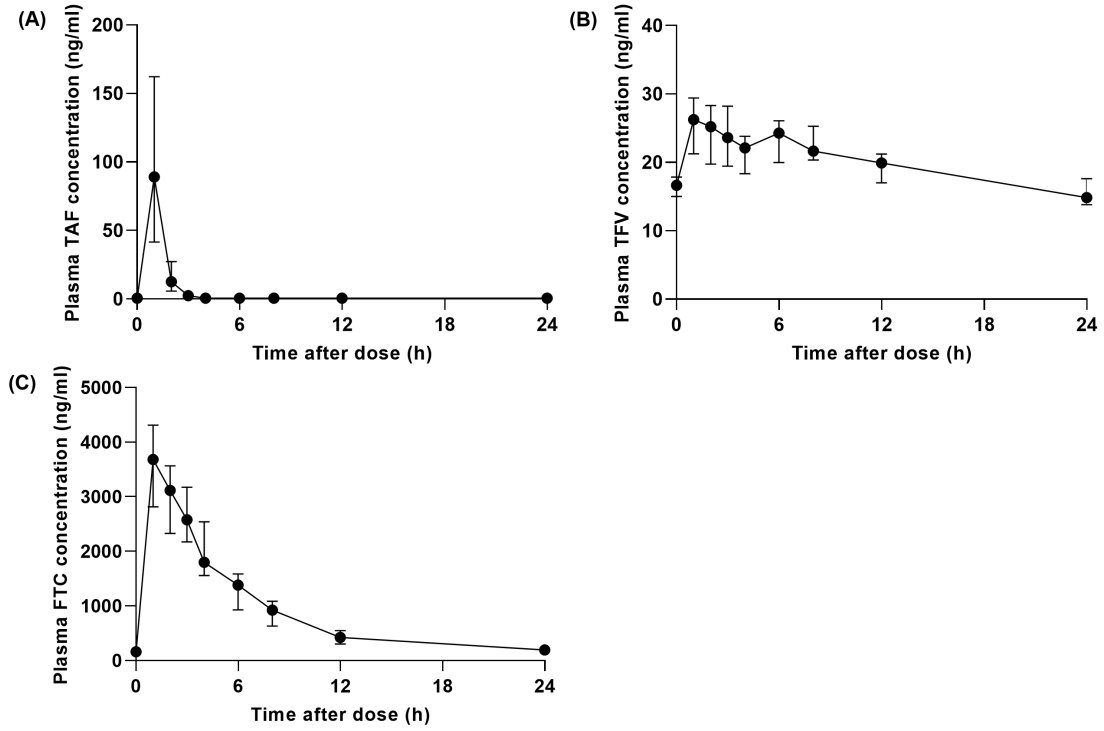


Figure 1. Pharmacokinetics of tenofovir alafenamide, tenofovir, and emtricitabine in plasma. (A) tenofovir alafenamide (TAF), **(B)** tenofovir (TFV), **(C)** emtricitabine (FTC). The data are illustrated as the median ± interquartile range.

Table 2. Pharmacokinetics of intracellular tenofovir-diphosphate and emtricitabine-triphosphate

Time after doses (hours)	0	1	2	3	4	6	8	12	24
TFV-DP (fmol/ punches)									
Median	1,214	1,161	1,335	1,086	1,354	1,113	1,373	1,191	1,597
75% Percentile	1,540	1,645	1,673	1,963	1,949	2,170	2,372	2,489	2,584
25% Percentile	1,066	782.9	966	837.6	965.4	910.7	1,002	802.5	830.9
FTC-TP (fmol/ punches)									
Median	1,550	2,316	1,818	2,166	2,539	1,725	2,657	1,527	1,640
75% Percentile	2,455	3,441	3,352	3,886	4,060	5,026	4,412	4,497	4,276
25% Percentile	836.1	1,027	1,451	1,153	936	1,069	972.3	977.5	607.6

TP using DBS (*15,18*); however to our knowledge (*19*), this is the first study to compare plasma and intracellular concentrations of the analytes of interest and their corresponding metabolites among Japanese patients taking BIC/FTC/TAF. Our results subsequently confirmed that the half-lives of intracellular TFV-DP and FTC-TP were significantly long, whereas their concentrations were stable and independent of the plasma concentrations of TAF, TFV, and FTC.

The plasma $T_{1/2}$ of TFV was long (31.6 h) or almost stable after FTC/TAF. The reason behind the long TFV $T_{1/2}$ could be explained as follows (*20*): After TAF is absorbed in plasma, it directly enters target cells, is subjected to ester hydrolysis by cathepsin A to TFV, and is subsequently phosphorylated to TFV-DP or slowly released from the cells into the plasma. Therefore, TFV has a low C_{max}, whereas its $T_{1/2}$ is stable. Therefore, plasma TFV concentrations could be used to monitor PrEP adherence, especially among PrEP users taking TFV/TAF. However, further studies on patients receiving FTC/TDF are necessary.

The efficacy of PrEP has been reported to be excellent in many previous studies and is recommended by several guidelines (*6,7*), provided that good adherence to treatment is maintained. Nonetheless, unlike HIV-1 treatment, which is currently based on a once-daily therapy strategy and where treatment success can be objectively assessed by plasma viral load, plasma drug concentrations among PrEP users would only be useful as markers if the dosing occurred on the same day. This might not be the case because they often take the medication before sexual intercourse, which might happen the day or night before.

According to our data, the plasma concentration of each drug did not correlate with the intracellular pharmacologically active metabolites. Since these intracellular metabolites have a significant longer duration, particularly after TDF/FTC or FTC/TAF dosing, TFV-DP remains in DBS for approximately 2 weeks. This results in a 25-fold accumulation from the

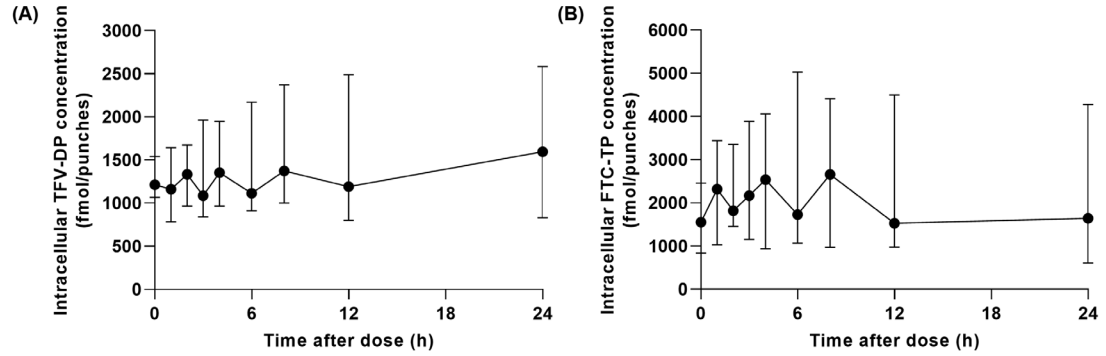


Figure 2. Pharmacokinetics of intracellular tenofovir-diphosphate and emtricitabine-triphosphate. (A) tenofovir-diphosphate (TFV-DP), **(B)** emtricitabine-triphosphate (FTC-TP). The data are illustrated as the median ± interquartile range.

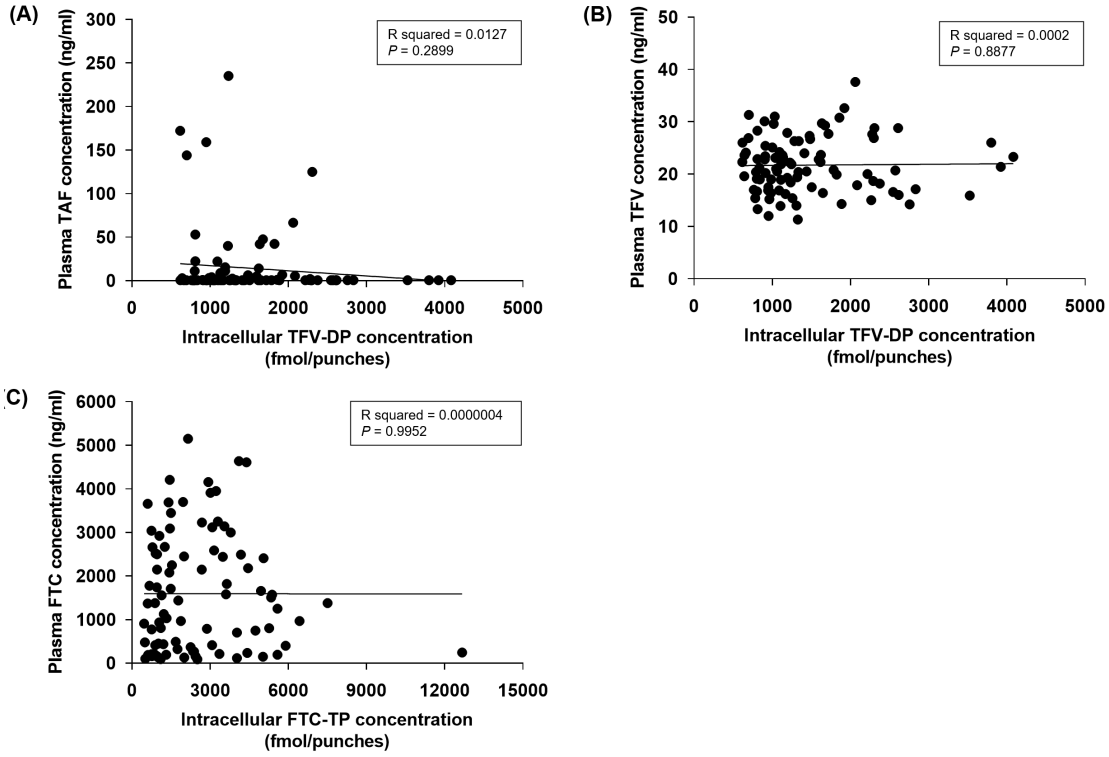


Figure 3. Correlations between plasma concentrations of tenofovir alafenamide, tenofovir, and emtricitabine and their corresponding intracellular drug concentrations. (A) tenofovir alafenamide (TAF) and tenofovir-diphosphate (TFV-DP), **(B)** tenofovir (TFV) and tenofovir-diphosphate (TFV-DP), **(C)** emtricitabine (FTC) and tenofovir-diphosphate (FTC-TP).

first dose to steady state, which can be used to reflect adherence levels over the past 1–3 months (*21,22*). Compared to TFV-DP, FTC-TP has a shorter $T_{1/2}$; therefore, its detectable levels could reflect recent dosing (*22*). Owing to this, if the concentrations of both TFV-DP and FTC-TP are high, the patient would have been in good adherence for a certain period of time. In the case of a low TFV-DP with high FTC-TP concentration, it could be an indication that the patient stopped taking PrEP in the past only recently became adherent. In contrast, that is, a patient with a high TFV-DP but low FTC-TP concentration, it could be assumed that such a patient has been adherent for a long time but has recently stopped taking PrEP. For the latter subgroup and those with undetectable levels of both drugs, counseling could be useful to further investigate the underlying reasons. Thus, intracellular TFV-DP and FTC-TP could serve as objective measures to assist clinicians in delivering patient-specific PrEP monitoring interventions.

This study had several limitations. First, the method used to measure intracellular TFV-DP and FTC-TP still needs to be standardized since the concentration of active metabolites, which could be as low as fmol, interferes with the background signal. Second, only FTC/TAF was examined in the plasma samples; however, FTC/TDF should also be analyzed. Third, the samples used in this study were obtained from patients who administered BIC/FTC/TAF. No drug interactions between BIC and FTC/TAF were reported, and in a predefined protocol, the samples were not specific for the FTC/TAF PK study.

In conclusion, intracellular FTV-DP and FTC-TP in DBS could be helpful indicators for monitoring PrEP adherence, due to their reflection prolonged plasma circulation. In addition to the clear advantages of DBS over conventional plasma analysis in terms of sampling and transportation, this study provides additional evidence to the current body of literature for its application in daily practice.

Acknowledgements

We thank the clinical and laboratory staff of AIDS Clinical Center, National Center for Global Health and Medicine for their helpful support.

Funding: This work was supported by Gilead Sciences Inc. USA (study number IN-JP-380-5724) and the Science and Technology Research Partnership for Sustainable Development (SATREPS) project funded by JICA and AMED.

Conflict of Interest: TSO has received research grants from ViiV Healthcare and Gilead Sciences, a drug for clinical research from Gilead Sciences, and an honorarium for lectures from ViiV Healthcare and Gilead Sciences. These funding sources had no impact on the study design, data collection, or interpretation. The salary of Yoshimi Deguchi was partially paid from the study grant "IN-JP-380-5724", and HTT was an overseas postgraduate student supported at the full expense of the Japanese Government under the SATREPS project.

References

1. Pharmacoeconomic Review Report: Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/FTC/TAF) (Biktarvy): (Gilead Sciences Canada, Inc.): Indication: A complete regimen for the treatment of HIV-1 infection in adults with no known substitution associated with resistance the individual components of Biktarvy. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2018. *http://www.ncbi.nlm.nih.gov/books/NBK539546/* (accessed May 8, 2023)
2. Gilead. Biktarvy, Bictegravir/Emtricitabine/Tenofovir Alafenamide: EU SUMMARY OF PRODUCT CHARACTERISTICS. 2018. *https://www.ema.europa.eu/en/documents/product-information/biktarvy-epar-product-information_en.pdf* (accessed May 8, 2023)
3. Kawashima A, Trung HT, Watanabe K, Takano M, Deguchi Y, Kinoshita M, Uemura H, Yanagawa Y, Gatanaga H, Kikuchi Y, Oka S, Tsuchiya K. Pharmacokinetics of bictegravir in older Japanese people living with HIV-1. Microbiol Spectr. 2023; 11:e0507922.
4. Saag MS, Benson CA, Gandhi RT, *et al.* Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 Recommendations of the International Antiviral Society-USA Panel. JAMA. 2018; 320:379-396.
5. European AIDS Clinical Society (EASC). Guidelines version 10.1. 2020. *https://www.eacsociety.org/media/guidelines-10.1_30032021_1.pdf* (accessed May 8, 2023)
6. U.S. Center for Disease Control. Preexposure prophylaxis for the prevention of HIV infection in the United States - 2021 update, a clinical practice guideline. *https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf* (accessed May 17, 2023)
7. World Health Organization. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. *https://www.who.int/publications-detail-redirect/9789240031593* (accessed May 17, 2023)
8. Grant RM, Anderson PL, McMahan V, *et al.* Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: A cohort study. Lancet Infect Dis. 2014; 14:820-829.
9. Marrazzo JM, Ramjee G, Richardson BA, *et al.* Tenofovir-based preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2015; 372:509-518.
10. de Lastours V, Fonsart J, Burlacu R, Gourmel B, Molina JM. Concentrations of tenofovir and emtricitabine in saliva: implications for preexposure prophylaxis of oral HIV acquisition. Antimicrob Agents Chemother. 2011; 55:4905-4907.
11. Seifert SM, Chen X, Meditz AL, *et al*. Intracellular tenofovir and emtricitabine anabolites in genital, rectal, and blood compartments from first dose to steady state. AIDS Res Hum Retroviruses. 2016; 32:981-991.
12. Koenig HC, Mounzer K, Daughtridge GW, Sloan CE, Lalley-Chareczko L, Moorthy GS, Conyngham SC, Zuppa AF, Montaner LJ, Tebas P. Urine assay for tenofovir to monitor adherence in real time to tenofovir disoproxil fumarate/emtricitabine as pre-exposure prophylaxis. HIV Med. 2017; 18:412-418.
13. Fonsart J, Saragosti S, Taouk M, *et al.* Single-dose pharmacokinetics and pharmacodynamics of oral tenofovir and emtricitabine in blood, saliva and rectal tissue: a sub-study of the ANRS IPERGAY trial. J Antimicrob Chemother. 2017; 72:478-485.
14. Brooks KM, Anderson PL. Pharmacologic-based methods of adherence assessment in HIV prevention. Clin Pharmacol Ther. 2018; 104:1056-1059.
15. Zheng JH, Rower C, McAllister K, Castillo-Mancilla J, Klein B, Meditz A, Guida LA, Kiser JJ, Bushman LR, Anderson PL. Application of an intracellular assay for determination of tenofovir-diphosphate and emtricitabine-triphosphate from erythrocytes using dried blood spots. J Pharm Biomed Anal. 2016; 122:16-20.
16. Podany AT, Bares SH, Havens J, Dyavar SR, O'Neill J, Lee S, Fletcher CV, Swindells S, Scarsi KK. Plasma and intracellular pharmacokinetics of tenofovir in patients switched from tenofovir disoproxil fumarate to tenofovir alafenamide. AIDS. 2018; 32:761-765.
17. Yager J, Castillo-Mancilla J, Ibrahim ME, Brooks KM, McHugh C, Morrow M, McCallister S, Bushman LR, MaWhinney S, Kiser JJ, Anderson PL. Intracellular tenofovir-diphosphate and emtricitabine-triphosphate in dried blood spots following tenofovir alafenamide: The TAF-DBS study. J Acquir Immune Defic Syndr. 2020; 84:323-330.
18. Schauer AP, Sykes C, Cottrell ML, Prince H, Kashuba ADM. Validation of an LC-MS/MS assay to simultaneously monitor the intracellular active metabolites of tenofovir, emtricitabine, and lamivudine in dried blood spots. J Pharm Biomed Anal. 2018; 149:40-45.

19. Zhang H. A study evaluating the pharmacokinetics, safety, and tolerability of the bictegravir/emtricitabine/tenofovir alafenamide (B-F-TAF) single tablet regimen (STR) in Japanese subjects. 2017. *https://www.abstract-archive.org/Abstract/Share/75616* (accessed June 3, 2023)
20. Ray AS, Fordyce MW, Hitchcock MJM. Tenofovir alafenamide: A novel prodrug of tenofovir for the treatment of human immunodeficiency virus. Antiviral Res. 2016; 125:63-70.
21. Castillo-Mancilla JR, Zheng JH, Rower JE, Meditz A, Gardner EM, Predhomme J, Fernandez C, Langness J, Kiser JJ, Bushman LR, Anderson PL. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. AIDS Res Hum Retroviruses. 2013; 29:384-390.
22. Anderson PL, Liu AY, Castillo-Mancilla JR, Gardner EM, Seifert SM, McHugh C, Wagner T, Campbell K, Morrow M, Ibrahim M, Buchbinder S, Bushman LR, Kiser JJ, MaWhinney S. Intracellular tenofovir-diphosphate and emtricitabine-triphosphate in dried blood spots following directly observed therapy. Antimicrob Agents Chemother. 2017; 62:e01710-17.

Received May 18, 2023; Revised June 5, 2023; Accepted June 16, 2023.

Released online in J-STAGE as advance publication July 28, 2023.

**Address correspondence to*:
Hieu Trung Tran, AIDS Clinical Center, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: thieutran@acc.ncgm.go.jp

Global Health & Medicine. 2023; 5(4):223-228.
ORIGINAL ARTICLE
DOI: 10.35772/ghm.2023.01008

The reverse shock index multiplied by the Glasgow Coma Scale score can predict the need for initial resuscitation in patients suspected of sepsis

Wataru Matsuda*, Akio Kimura, Tatsuki Uemura

Department of Emergency Medicine and Critical Care, Center Hospital of the National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: For patients suspected of sepsis, early recognition of the need for initial resuscitation is key in management. This study evaluated the ability of a modified shock index — the reverse shock index multiplied by the Glasgow Coma Scale score (rSIG) — to predict the need for initial resuscitation in patients with sepsis. This retrospective study involved adults with infection who were admitted to a Japanese tertiary care hospital from an emergency department between January and November 2020. The rSIG, modified Early Warning Score (MEWS), quick Sequential Organ Failure Assessment (qSOFA), and original shock index (SI) values were recorded using initial vital signs. The primary outcome was the area under the receiver-operating characteristic curve (AUROC) for the composite outcome consisting of vasopressor use, mechanical ventilation, and 72-h mortality. Secondary outcomes were the AUROCs for each component of the primary outcome and 28-day mortality. As a result, the primary outcome was met by 67 of the 724 patients (9%). The AUROC was significantly higher for the rSIG than for the other tools (rSIG 0.84 [0.78 – 0.88]; MEWS 0.78 [0.71 – 0.84]; qSOFA 0.72 [0.65 – 0.79]; SI 0.80 [0.74 – 0.85]). Compared with MEWS and qSOFA, the rSIG also had a higher AUROC for vasopressor use and mechanical ventilation, but not for 72-h mortality or in-hospital mortality. The rSIG could be a simple and reliable predictor of the need for initial resuscitation in patients suspected of sepsis.

***Keywords*:** shock index, sepsis, early warning score, emergency department, resuscitation, triage

Introduction

Early recognition is key in the management of sepsis because initial resuscitation for sepsis or septic shock, namely, a sepsis bundle, should be recommended to start immediately. Japanese clinical practice guidelines recommend initial assessment based on vital signs when sepsis is suspected (*1*). However, although vital signs can be measured quickly, it remains unclear how they should be evaluated when used to determine the need for early resuscitation.

Because qSOFA — a simply predictive tools for sepsis using vital signs — have low sensitivity, international guidelines recommend using an early warning method when screening for sepsis, such as the modified Early Warning Score (MEWS) (*2*). However, the MEWS is time-consuming and difficult to implement unless trained medical staff and well-equipped facilities are available. Furthermore, although the MEWS is a good predictor of in-hospital mortality (*3-5*), admission to an intensive care unit (ICU) (*4,5*), and a diagnosis of sepsis (*6,7*), it is unclear whether it is a good predictor of the need for initial resuscitation.

Adherence to the sepsis bundle is low worldwide (*8-19*) because it requires significant medical resources to achieve adherence. Achieving a bundle in all patients with sepsis places a high burden on medical staff, so it makes sense to prioritize high-risk sepsis patients for initial resuscitation.

The shock index (SI) or a modified SI has also been used for the initial assessment of sepsis (*20-24*). The SI is considered useful for identifying patients with sepsis who require initial resuscitation because it is a hemodynamic assessment. Among the modified SIs in use, a simple modified SI developed for trauma patients, the reverse shock index multiplied by the Glasgow Coma Scale score (rSIG), has been reported to be superior to conventional scoring systems in predicting short-term mortality (*25-31*), need for massive transfusion (*28,32*), and need for early intervention (*28,33,34*). Despite its simplicity, we hypothesized that the rSIG would be better than conventional tools for identifying patients with sepsis who require intensive organ support in the early phase. Therefore, in this study, we evaluated whether the rSIG would be a better predictor of the need for vasopressor use, the need for mechanical ventilation,

or of death within the initial 72 h after triage when compared with the MEWS, quick Sequential Organ Failure Assessment (qSOFA), and SI.

Materials and Methods

Ethical approval and informed consent

The study was approved by the ethics committee at our hospital (approval number: NCGM-S-004384-00) and followed the principles of the Declaration of Helsinki. Informed consent was obtained using the opt-out method *via* the hospital website.

Study design and settings

This retrospective single-center study was performed at an urban tertiary care hospital in Japan. About 20,000 patients visit its emergency department each year, and more than half arrive by ambulance. This study included patients admitted to the hospital for infections from the emergency department. All patients with infection were evaluated for sepsis and initially treated in accordance with national and international guidelines by emergency physicians. Exclusion criteria were transfer from another hospital, less than 18 years of age, a definitive diagnosis of COVID-19, and missing data for vital signs at triage.

Data collection

Information was collected on age, sex, site of infection, vital signs, initial Sequential Organ Failure Assessment (SOFA) score, and 28-day and in-hospital mortality. Vital signs included the first values recorded in the hospital. The SOFA score was assessed at the time of admission to the ICU or a ward.

The primary outcome was the area under the receiver-operating characteristic curve (AUROC) for the composite events consisting of vasopressor use, mechanical ventilation, and 72-h mortality. Secondary outcomes were each component of the composite events of primary outcome and 28-day mortality.

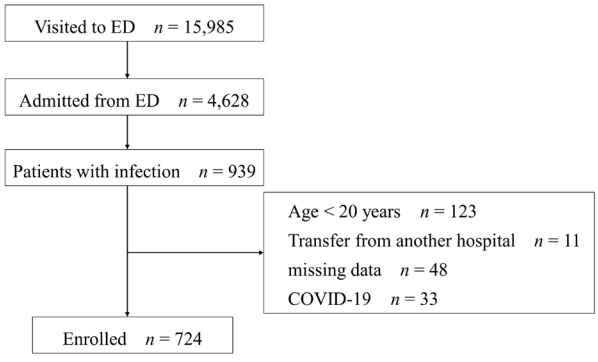


Figure 1. Flow of participants through the study. ED, emergency department

Statistical analysis

Categorical variables were examined using Fisher's exact test and continuous variables using the Mann–Whitney *U* test. Receiver-operating characteristic curves (ROC) were generated to visualize the impact of shifting the positive cutoff value on true-positive (sensitivity) and false-positive (1 − specificity) rates. The AUROCs were compared using the technique described by DeLong *et al.* (*35*). Statistical significance was set at $p < 0.05$ in all analyses. Sensitivity analyses were performed based on age < 80 years, without treatment limitation, and optimal cut-off values. The optimal cut-off values were defined by the value when the AUROC of each score was maximum. All statistical analyses was performed using R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria) and JMP Pro version 15 (SAS Institute Inc., Cary, NC). We were not able to impute missing data for vital signs because they were probably not random.

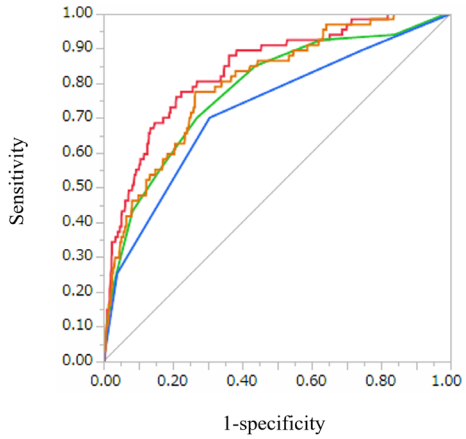
Results

A total of 724 patients were enrolled between January and November 2020 (Figure 1). Most patients were elderly and one third had a treatment limitation, such as a do-not-attempt resuscitation or intubation order (Table 1). Overall, 455 patients (63%) were diagnosed with sepsis

Table 1. Patient characteristics

Variable	*n* = 724
Age, years, median [IQR]	81 [71, 88]
Male, *n* (%)	376 (52)
Vital signs	
Systolic blood pressure, mmHg, median [IQR]	131 [111, 150]
Heart rate, beats/min, median [IQR]	96 [82, 111]
Glasgow Coma Scale score, median [IQR]	15 [13, 15]
Respiratory rate, beats/min, median [IQR]	20 [18, 24]
Body temperature, °C, median [IQR]	37.7 [36.9, 38.6]
Initial SOFA score, median [IQR]	3 [1, 4]
Main sites of infection, *n* (%)	
Respiratory	322 (44)
Urinary	161 (22)
Abdomen	133 (18)
Soft tissue	49 (7)
Other	59 (8)
Sepsis, *n* (%)	455 (63)
Septic shock, *n* (%)	33 (5)
Treatment limitation, *n* (%)	256 (35)
Composite outcome	
Any, *n* (%)	67 (9)
Vasopressor use within 72 h, *n* (%)	44 (6)
Mechanical ventilation within 72 h, *n* (%)	31 (4)
Death within 72 h, *n* (%)	22 (3)
Death at day 28, *n* (%)	61 (8)
In-hospital death, *n* (%)	85 (12)

*Categorical variables were analyzed by Fisher's exact test and continuous variables by the Mann–Whitney *U* test. Sepsis and septic shock were diagnosed based on the Sepsis-3 definitions. SOFA, Sequential Organ Failure Assessment.



	AUROC	Lower 95%	Upper 95%
rSIG	0.84	0.78	0.88
MEWS	0.78	0.71	0.84
qSOFA	0.72	0.65	0.79
SI	0.80	0.74	0.85

	Chi square	*p* value
rSIG *vs.* MEWS	5.95	0.015
rSIG *vs.* qSOFA	0.17	< 0.001
rSIG *vs.* SI	5.33	0.021

Figure 2. Comparisons of receiver operating characteristic (ROC) curves for the composite outcome consisting of vasopressor use, mechanical ventilation, and 72-h mortality. rSIG, reverse shock index multiplied by Glasgow Coma Scale score; MEWS, modified Early Warning Score; qSOFA, quick Sequential Organ Failure Assessment; SI, shock index; AUROC, area under ROC. Red, green, blue and yellow lines indicate rSIG, MEWS, qSOFA and SI respectively.

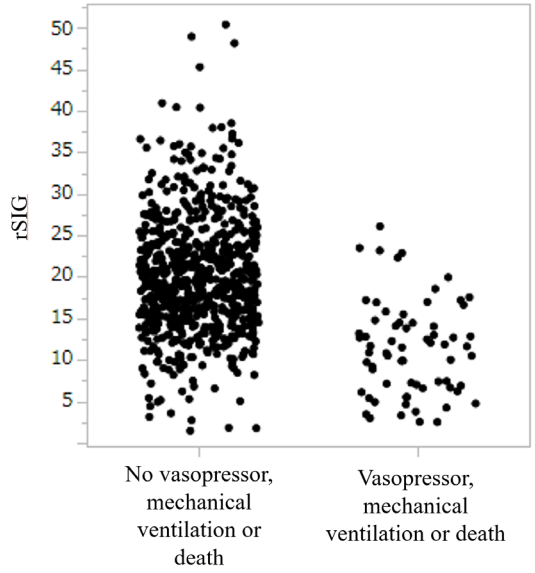


Figure 3. Distribution of rSIG values according to whether or not the composite events of primary outcome was met. rSIG, reverse shock index multiplied by the Glasgow Coma Scale score. The composite events included vasopressor use, mechanical ventilation, and 72-h death.

and 33 (5%) with septic shock according to the SEPSIS-3 criteria. In total, 67 patients (9%) required treatment with a vasopressor or mechanical ventilation or died within 72 h of triage.

Primary outcome

In terms of the primary outcome, the AUROCs for the rSIG, MEWS, qSOFA, and SI were 0.84 (0.78 – 0.88), 0.78 (0.71 – 0.84), 0.72 (0.65 – 0.79), and 0.80 (0.74 – 0.85), respectively (Figure 2). The AUROC for the rSIG was significantly higher than that of MEWS ($p = 0.015$), qSOFA ($p < 0.001$) and SI ($p = 0.021$). Figure 3 shows the distribution of rSIG values according to whether or not the composite events of primary outcome were met.

Table 2. Results of sensitivity analyses

Variable	AUROC	95% CI	*p* value
Age < 80 years, *n* = 319			
rSIG	0.87	0.79 – 0.92	
vs. MEWS	0.75	0.66 – 0.83	0.005
vs. qSOFA	0.75	0.66 – 0.83	< 0.001
vs. SI	0.79	0.69 – 0.86	0.008
Without treatment limitation, *n* = 468			
rSIG	0.86	0.79 – 0.91	
vs. MEWS	0.77	0.68 – 0.84	0.003
vs. qSOFA	0.73	0.65 – 0.81	< 0.001
vs. SI	0.81	0.73 – 0.86	0.004
Optimal cut-off value*			
rSIG ≤ 15	0.77	0.72 – 0.82	
vs. MEWS ≥ 5	0.72	0.66 – 0.77	0.028
vs. qSOFA ≥ 2	0.70	0.64 – 0.75	0.013
vs. SI ≤ 0.9	0.71	0.65 – 0.77	0.027

*Optimal cut-off values were defined by the value when each AUROC was maximum. rSIG, reverse shock index multiplied by Glasgow Coma Scale score; MEWS, modified Early Warning Score; qSOFA, quick Sequential Organ Failure Assessment; SI, shock index.

Table 2 showed the results of the sensitivity analyses. In subgroups of patients with age < 80 years ($n = 319$) and patients without treatment limitation ($n = 468$), The AUROC for the rSIG was significantly higher than that of the other tools.

The optimal rSIG, MEWS, qSOFA, and SI cut-off values were 14.8, 5, 2, and 0.87, respectively. Sensitivity and specificity of rSIG ≤ 15 were 0.78 and 0.77, respectively. When individual optimal cutoff values were used, the AUROCs for the rSIG ≤ 15, MEWS ≥ 5, qSOFA ≥ 2 and SI ≤ 0.9 were 0.77 (0.72 – 0.82), 0.72 (0.66 – 0.77), 0.70 (0.64 – 0.75), and 0.71 (0.65 – 0.77), respectively (Table 2). The AUROC for the rSIG was significantly higher than that of MEWS ($p = 0.028$), qSOFA ($p = 0.013$) and SI ($p = 0.027$).

Secondary outcomes

Table 3. Results for secondary outcomes

Variable	AUROC	95% CI	*p* value
Vasopressor use within 72 h			
rSIG	0.85	0.78 – 0.90	
vs. MEWS	0.78	0.70 – 0.84	0.017
vs. qSOFA	0.73	0.64 – 0.81	< 0.001
vs. SI	0.83	0.76 – 0.88	0.26
Mechanical ventilation within 72 h			
rSIG	0.82	0.73 – 0.88	
vs. MEWS	0.74	0.65 – 0.82	0.052
vs. qSOFA	0.67	0.58 – 0.74	< 0.001
vs. SI	0.77	0.68 – 0.84	0.07
Death at 72 h			
rSIG	0.86	0.76 – 0.93	
vs. MEWS	0.86	0.77 – 0.91	0.87
vs. qSOFA	0.86	0.78 – 0.91	0.88
vs. SI	0.82	0.70 – 0.90	0.11
Death at 28 d			
rSIG	0.75	0.68 – 0.81	
vs. MEWS	0.71	0.64 – 0.77	0.07
vs. qSOFA	0.71	0.63 – 0.78	0.13
vs. SI	0.72	0.65 – 0.78	0.06

rSIG, reverse shock index multiplied by Glasgow Coma Scale score; MEWS, modified Early Warning Score; qSOFA, quick Sequential Organ Failure Assessment; SI, shock index.

Table 3 shows the secondary outcomes. The AUROC for vasopressor use within 72 h was significantly higher for the rSIG (0.85 [0.78 – 0.90]) than for the MEWS (0.78 [0.70 – 0.84], $p = 0.017$) or qSOFA (0.73 [0.64 – 0.81], $p < 0.001$) but not for the SI (0.83 [0.76 – 0.88], $p = 0.26$). The AUROC for mechanical ventilation within 72 h was significantly higher for the rSIG (0.82 [0.73 – 0.88)) than for the qSOFA (0.67 [0.58 – 0.74], $p < 0.001$) but not for the MEWS (0.74 [0.65 – 0.82], $p = 0.052$) or SI (0.77 [0.68 – 0.84], $p = 0.07$). There was no significant difference in the AUROCs for 72-h or 28-day mortality between rSIG and the other tools (72-h mortality: rSIG 0.86 (0.76 – 0.93), MEWS 0.86 (0.77 – 0.91), qSOFA 0.86 (0.78 – 0.91), SI 0.82 (0.70 – 0.90), 28-day mortality: rSIG 0.75 (0.68 – 0.81), MEWS 0.71 (0.64 – 0.77), qSOFA 0.71 (0.63 – 0.78), SI 0.72 (0.65 – 0.78)).

Discussion

In this study, the rSIG was superior in predicting the need for intensive organ support and death in the early phase in patients with infection compared with the MEWS, qSOFA, and SI. Furthermore, the performance of the rSIG was similar to or better than the qSOFA and MEWS in terms of vasopressor use, mechanical ventilation and short-term mortality. Although the rSIG has been used mainly for trauma, the results of this study suggest that it may also be useful for patients with infection. The optimal rSIG cut-off value reported for trauma patients ranges from 9.5 to 14.8 (*26-28,32*), which is similar to that in our study. Considering that vital signs are not disease-specific parameters, we believe that our result is reasonable.

Interestingly, the rSIG was found to have a higher AUROC for need of mechanical ventilation, even without inclusion of the respiratory rate which is usually an important parameter in the clinical assessment. The respiratory rate is often difficult to measure accurately (*36,37*), therefore , it was suitable to be a factor in inadequate assessment. Body temperature can also lead to misjudgments: sepsis with fever has been shown to have a better outcome than sepsis without fever (*38*), in contrast with the MEWS, which scores higher for hyperthermia. Not including the respiratory rate and body temperature measurements in the rSIG may have contributed to its high predictive performance.

Japan is an aging society and most of our patients were elderly. Interpretation of vital signs is complicated in the elderly for several reasons, including underlying medical conditions and use of antihypertensive medications. For example, it has been reported that the relationship between vital signs and outcome in patients with sepsis differs between the elderly and non-elderly (*39*). Therefore, we performed a sensitivity analysis by subgroup, namely, for age < 80 years and presence of treatment limitations. The results were similar to the analysis of all patients, which increases the generalizability of our findings.

Given that the rSIG was significantly more predictive of vasopressor use than the MEWS or qSOFA, it may be better at predicting the need for initial resuscitation. Triggering initial resuscitation based on the rSIG value could lead to earlier management (*e.g.*, antibiotic therapy, use of a vasopressor, or admission to the ICU). Although a matter of controversy in patients without shock, there is some evidence suggesting that every 1-h delay in administration of antibiotics increases the likelihood of mortality in patients with shock (*40-42*). Yet, adherence to the sepsis bundle is particularly low in patients with septic shock because of the time required to perform procedures such as intubation or insertion of a central venous catheter. Therefore, early recognition is particularly important in patients with septic shock.

This study has some limitations. First, screening was performed according to the final diagnosis because the study was retrospective in nature. Therefore, we were unable to include patients who were suspected of having an infection at triage but were ultimately determined to be free of infection. Second, we excluded patients with COVID-19 because the pattern of organ failure in COVID-19 may differ from that in conventional sepsis. Also, owing to local circumstances, it was not possible to enroll a sufficient number of patients with COVID-19 to be able to evaluate the triage tool in this cohort. However, international sepsis guidelines have been published for conventional sepsis and sepsis in patients with COVID-19 (*2,43*). Based on the above, we consider it appropriate to distinguish between conventional sepsis and COVID-19 at this time. Third, we included only hospitalized patients because we were unable to

investigate outcomes in patients who did not require hospitalization.

Conclusions

The rSIG was a significantly better predictor of the need for a vasopressor, the need for mechanical ventilation, and death within 72 h of triage in patients with infection at an emergency department. The rSIG could be a simple and reliable predictor of the need for initial resuscitation in patients with sepsis.

Funding: This work was supported in part by a Grant-in-Aid for Research from the National Center for Global Health and Medicine (20A3002).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Egi M, Ogura H, Yatabe T, *et al.* The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020 (J-SSCG 2020). J Intensive Care. 2021; 9:53.
2. Evans L, Rhodes A, Alhazzani W, *et al.* Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021; 47:1181-247.
3. Churpek MM, Snyder A, Han X, Sokol S, Pettit N, Howell MD, Edelson DP. Quick sepsis-related organ failure assessment, systemic inflammatory response syndrome, and early warning scores for detecting clinical deterioration in infected patients outside the intensive care unit. Am J Respir Crit Care Med. 2017; 195:906-911.
4. Usul E, Korkut S, Kayipmaz AE, Halici A, Kavalci C. The role of the quick sequential organ failure assessment score (qSOFA) and modified early warning score (MEWS) in the pre-hospitalization prediction of sepsis prognosis. Am J Emerg Med. 2021; 41:158-162.
5. Sabir L, Ramlakhan S, Goodacre S. Comparison of qSOFA and Hospital Early Warning Scores for prognosis in suspected sepsis in emergency department patients: A systematic review. Emerg Med J. 2022; 39:284-294.
6. Wattanasit P, Khwannimit B. Comparison of the accuracy of early warning scores with qSOFA and SIRS for predicting sepsis in the emergency department. Am J Emerg Med. 2021; 46:284-288.
7. McGrath SP, Perreard I, MacKenzie T, Calderwood M. Improvement of sepsis identification through multi-year comparison of sepsis and early warning scores. Am J Emerg Med. 2022; 51:239-247.
8. Townsend SR, Phillips GS, Duseja R, Tefera L, Cruikshank D, Dickerson R, Nguyen HB, Schorr CA, Levy MM, Dellinger RP, Conway WA, Browner WS, Rivers EP. Effects of compliance with the early management bundle (SEP-1) on mortality changes among Medicare beneficiaries with sepsis: A propensity score matched cohort study. Chest. 2022; 161:392-406.
9. Umemura Y, Abe T, Ogura H, *et al*. Hour-1 bundle adherence was associated with reduction of in-hospital mortality among patients with sepsis in Japan. PLoS One. 2022; 17:e0263936.
10. Milano PK, Desai SA, Eiting EA, Hofmann EF, Lam CN, Menchine M. Sepsis bundle adherence is associated with improved survival in severe sepsis or septic shock. West J Emerg Med. 2018; 19:774-781.
11. Ranzani OT, Monteiro MB, Besen B, Azevedo LCP. Association of sepsis diagnosis at daytime and on weekdays with compliance with the 3-hour sepsis treatment bundles. A multicenter cohort study. Ann Am Thorac Soc. 2020; 17:980-987.
12. Machado FR, Ferreira EM, Schippers P, *et al*. Implementation of sepsis bundles in public hospitals in Brazil: A prospective study with heterogeneous results. Crit Care. 2017; 21:268.
13. Sonis JD, Benzer TI, Black L, Filbin MR, Hayes BD, Hibbert KA, Kraus C, Raja AS, Temin E, Vareschi M, White BA, Wilcox SR, Aaronson EL. Utilization of a multidisciplinary emergency department sepsis huddle to reduce time to antibiotics and improve SEP-1 compliance. Am J Emerg Med. 2020; 38:2400-2404.
14. Hu B, Xiang H, Dong Y, Portner E, Peng Z, Kashani K. Timeline of sepsis bundle component completion and its association with septic shock outcomes. J Crit Care. 2020; 60:143-151.
15. Baghdadi JD, Brook RH, Uslan DZ, Needleman J, Bell DS, Cunningham WE, Wong MD. Association of a care bundle for early sepsis management with mortality among patients with hospital-onset or community-onset sepsis. JAMA Intern Med. 2020; 180:707-716.
16. Prachanukool T, Sanguanwit P, Thodamrong F, Suttapanit K. The 28-day mortality outcome of the complete hour-1 sepsis bundle in the emergency department. Shock. 2021; 56:969-974.
17. Wang L, Ma X, He H, Su L, Guo Y, Shan G, Wang Y, Zhou X, Liu D, Long Y; China National Critical Care Quality Control Center Group. Compliance with the Surviving Sepsis Campaign guideline 1-hour bundle for septic shock in China in 2018. Ann Transl Med. 2021; 9:278.
18. Bahar İ, Oksuz H, Şenoğlu N, Demirkiran H, Aydoğan M, Tomak Y, Çömez M, Bayrakçı S, Gönüllü E, Berktaş M. Compliance with the surviving sepsis campaign bundle: A multicenter study from Turkey. Cureus. 2021; 13:e14989.
19. You JS, Park YS, Chung SP, *et al.* Relationship between time of emergency department admission and adherence to the Surviving Sepsis Campaign bundle in patients with septic shock. Crit Care. 2022; 26:43.
20. Berger T, Green J, Horeczko T, Hagar Y, Garg N, Suarez A, Panacek E, Shapiro N. Shock index and early recognition of sepsis in the emergency department: pilot study. West J Emerg Med. 2013; 14:168-174.
21. Althunayyan SM, Alsofayan YM, Khan AA. Shock index and modified shock index as triage screening tools for sepsis. J Infect Public Health. 2019; 12:822-826.
22. Middleton DJ, Smith TO, Bedford R, Neilly M, Myint PK. Shock index predicts outcome in patients with suspected sepsis or community-acquired pneumonia: A systematic review. J Clin Med. 2019; 8:1144.
23. Jouffroy R, Pierre Tourtier J, Gueye P, Bloch-Laine E, Bounes V, Debaty G, Boularan J, Carli P, Vivien B. Prehospital shock index to assess 28-day mortality for septic shock. Am J Emerg Med. 2020; 38:1352-1356.
24. Jouffroy R, Gilbert B, Thomas L, Bloch-Laine E, Ecollan P, Boularan J, Bounes V, Vivien B, Gueye PN. Association between prehospital shock index variation and 28-day

mortality among patients with septic shock. BMC Emerg Med. 2022; 22:87.
25. Kimura A, Tanaka N. Reverse shock index multiplied by Glasgow Coma Scale score (rSIG) is a simple measure with high discriminant ability for mortality risk in trauma patients: an analysis of the Japan Trauma Data Bank. Crit Care. 2018; 22:87.
26. Wu SC, Rau CS, Kuo SCH, Chien PC, Hsieh HY, Hsieh CH. The reverse shock index multiplied by Glasgow Coma Scale Score (rSIG) and prediction of mortality outcome in adult trauma patients: a cross-sectional analysis based on registered trauma data. Int J Environ Res Public Health. 2018; 15:2346.
27. Chu WT, Liao CH, Lin CY, Chien CY, Lin CC, Chang KW, Chen JH, Chen WL, Huang CC, Lim CJ, Chung JY. Reverse shock index multiplied by Glasgow Coma Scale (rSIG) predicts mortality in severe trauma patients with head injury. Sci Rep. 2020; 10:2095.
28. Lammers D, Conner J, Marenco C, Morte K, Martin M, Eckert M, *et al*. Optimal prospective predictors of mortality in austere environments. J Surg Res. 2020; 255:297-303.
29. Lammers DT, Marenco CW, Do WS, Conner JR, Horton JD, Martin MJ, Escobar MA Jr, Bingham JR, Eckert MJ. Pediatric adjusted reverse shock index multiplied by Glasgow Coma Scale as a prospective predictor for mortality in pediatric trauma. J Trauma Acute Care Surg. 2021; 90:21-26.
30. Lammers DT, Marenco CW, Morte KR, Conner JR, Horton JD, Barlow M, Martin MJ, Bingham JR, Eckert MJ, Escobar MA Jr. Addition of neurological status to pediatric adjusted shock index to predict early mortality in trauma: A pediatric Trauma Quality Improvement Program analysis. J Trauma Acute Care Surg. 2021; 91:584-589.
31. Frieler S, Lefering R, Gerstmeyer J, Drotleff N, Schildhauer TA, Waydhas C, Hamsen U; TraumaRegister DGU. Keeping it simple: the value of mortality prediction after trauma with basic indices like the reverse shock index multiplied by Glasgow Coma Scale. Emerg Med J. 2022; 39:912-917.
32. Lee YT, Bae BK, Cho YM, Park SC, Jeon CH, Huh U, Lee DS, Ko SH, Ryu DM, Wang IJ. Reverse shock index multiplied by Glasgow coma scale as a predictor of massive transfusion in trauma. Am J Emerg Med. 2021; 46:404-409.
33. Reppucci ML, Acker SN, Cooper E, Meier M, Stevens J, Phillips R, Moulton SL, Bensard DD. Improved identification of severely injured pediatric trauma patients using reverse shock index multiplied by Glasgow Coma Scale. J Trauma Acute Care Surg. 2022; 92:69-73.
34. Reppucci ML, Stevens J, Cooper E, Nolan MM, Jujare S, Acker SN, Moulton SL, Bensard DD. Use of reverse shock index times Glasgow coma scale (rSIG) to determine need for transfer of pediatric trauma patients to higher levels of care. J Pediatr Surg. 2023; 58:320-324.
35. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. Biometrics 1988; 44:837-845.
36. Philip KE, Pack E, Cambiano V, Rollmann H, Weil S, O'Beirne J. The accuracy of respiratory rate assessment by doctors in a London teaching hospital: A cross-sectional study. J Clin Monit Comput. 2015; 29:455-460.
37. Badawy J, Nguyen OK, Clark C, Halm EA, Makam AN. Is everyone really breathing 20 times a minute? Assessing epidemiology and variation in recorded respiratory rate in hospitalised adults. BMJ Qual Saf. 2017; 26:832-836.
38. Sundén-Cullberg J, Rylance R, Svefors J, Norrby-Teglund A, Björk J, Inghammar M. Fever in the emergency department predicts survival of patients with severe sepsis and septic shock admitted to the ICU. Crit Care Med. 2017; 45:591-599.
39. Shimazui T, Nakada TA, Walley KR, *et al.* Significance of body temperature in elderly patients with sepsis. Crit Care. 2020; 24:387.
40. Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, Lemeshow S, Osborn T, Terry KM, Levy MM. Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med. 2017; 376:2235-2244.
41. Liu VX, Fielding-Singh V, Greene JD, Baker JM, Iwashyna TJ, Bhattacharya J, Escobar GJ. The timing of early antibiotics and hospital mortality in sepsis. Am J Respir Crit Care Med. 2017; 196:856-863.
42. Im Y, Kang D, Ko RE, Lee YJ, Lim SY, Park S, Na SJ, Chung CR, Park MH, Oh DK, Lim CM, Suh GY; Korean Sepsis Alliance (KSA) investigators. Time-to-antibiotics and clinical outcomes in patients with sepsis and septic shock: A prospective nationwide multicenter cohort study. Crit Care. 2022; 26:19.
43. Alhazzani W, Møller MH, Arabi YM, *et al.* Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med. 2020; 46:854-887.

Received January 20, 2023; Revised May 30, 2023; Accepted July 21, 2023.

Released online in J-STAGE as advance publication July 28, 2023.

Address correspondence to:
Wataru Matsuda, Department of Emergency Medicine and Critical Care, Center Hospital of the National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku, Tokyo 162-8655, Japan.
E-mail: wmatsuda@hosp.ncgm.go.jp

Global Health & Medicine. 2023; 5(4):229-237.
ORIGINAL ARTICLE
DOI: 10.35772/ghm.2023.01061

Construction of a risk index system for the prediction of chronic post-surgical pain after video-assisted thoracic surgery for lung resection: A modified Delphi study

Zhimin Guo, Fei Zhong, Haihua Shu*

Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China.

Abstract: In the present study, several research methods were adopted, including literature retrieval, theoretical analysis, and qualitative research, and then the draft of the prognostic factors for the chronic post-surgical pain (CPSP) index system after video-assisted thoracoscopic surgery (VATS) for lung resection was constructed. A Delphi survey was used for the study of 24 experts in the field of pain from three different grade-A tertiary hospitals in Guangzhou, China. In the two rounds of survey, the experts rated these indicators for the importance and feasibility of measurement (round 1, n = 21 participants; round 2, n = 20). Finally, we calculated Kendall's W index as a measure of consensus. A general consensus was reached on predicting CPSP after VATS, consisting of 10 first-level domains and 64 second-level indicators, involving biological, psychological and social perspectives. This study provides a comprehensive draft of risk factors developed and identified by experts to inform research-based evidence on chronic pain. Increased clinical awareness and a full understanding of how to screen and identify people with CPSP problems may lead to earlier recognition of chronic pain and greater facilitation of professional prevention.

***Keywords*:** Delphi method, index system, risk factors, chronic post-surgical pain (CPSP)

Introduction

According to the 2022 cancer statistics report by the American Cancer Society (*1*), lung cancer has the second most new cancer cases, after prostate cancer in men and breast cancer in women. However, approximately 350 people die from lung cancer each day, more than those from prostate and breast cancers combined. Lung cancer has become the leading cause of cancer death. Similarly, as shown by the latest national cancer statistics in China, lung cancer ranks first among all cancers in terms of morbidity and mortality (*2*).

In the early stages of lung cancer, surgical resection is the only effective and widely accepted treatment (*3*). The incidences of developing chronic post-surgical pain (CPSP) from lung resection performed by general thoracotomy or less invasive video-assisted thoracic surgery (VATS) are 30–60% (*4*) and 40–60% (*5*), respectively. Despite advances in technology and medical care, the incidence and severity of CPSP after VATS have been reported to be similar to those of the traditional thoracotomy (*6*). Multiple pain management strategies had been applied during the perioperative period (before, during, and after surgery), but patients may still experience intense pain after VATS (*7*). What is more, acute pain after surgery can turn into chronic pain, and the mechanisms are complex and diverse (*8*). Lower quality of life and higher healthcare costs are accompanied with the extremely high frequencies of CPSP after VATS (*9*).

CPSP is now proposed in the International Classification of Diseases (ICD) 11th Revision (ICD-11), where it is classified as any pain related to the surgical area that persists for 3 months or longer after surgery, and other causes of pain, such as pre-existing pain conditions or infections, or malignancy, must be excluded (*10*). An in-depth understanding of the risk factors for CPSP may reduce morbidity, strengthen postoperative pain management, and ultimately improve patients' quality of life (*11*). Despite a huge number of research reports, there are no final conclusions and clear definitions on the incidence and severity of CPSP as well as on pain-related factors after VATS (*11,12*). The wide variability in risk factors may be due to different and appropriate methods of analysis (*9,13*), as well as the exclusion or short-listing of some potential risk factors, such as anxiety, depression, and social status (*14,15*). In a word, identification of patients at risk for chronic pain remains inadequate and challenging (*13,16*).

Previous research has suggested that an ideal prediction model for chronic pain is a thorough clinical survey that would include preoperative, intraoperative

and postoperative data (*17*). Some researchers have suggested that it is time to establish core risk factors for CPSP, which should encompass demographic, pain, clinical, surgery-related, and psychological domains (*13*). However, not all risk factors for CPSP after VATS have been taken into account, and no such study has been published so far.

The Delphi method is applied in various fields, especially in health care and nursing, to systematically integrate uncertain and incomplete issues from experts with research or practice backgrounds. The goal of this technique is to identify general statements, and consequently to reach a group consensus using previously determined criteria (*18,19*). Generally speaking, the Delphi method contains four key features, namely anonymity, iteration, controlled feedback, and the statistical aggregation of group response (*20*). It is constructed through a series of questionnaires and typically 2–3 iterations among experts in the relevant fields, without face-to-face communication, and then controlled feedback is presented in the form of statistical summary in each round. The modified Delphi technique focuses on collecting items from the literature review, and scoring each item in the questionnaire on a Likert scale, while suggestions are encouraged in each round. After the rounds, the items are modified or added to, and disputes will be reduced. In the end, a core outcome set is established, and measurable outcomes or topics in clinical trials are identified (*21,22*).

The objective of this study is to construct a core risk index system for CPSP after VATS, and to summarize and synthesize the current evidence on risk factors for CPSP through a Delphi survey consulting experts in related fields.

Materials and Methods

Design

Since data about CPSP predictors have been extensively reported and are available, we carried out a modified Delphi survey (Figure 1), which allowed us to construct a first draft of the risk index for CPSP through a literature review. The modified recommendation for the Conducting and REporting of DElphi Studies (CREDES) was used to guide the study (*23*). This study was approved by the Ethics Committee of Guangdong Provincial General's Hospital (KYH202200801).

Literature review and preliminary list of indicators

The literature review, including retrospective and prospective studies, randomized controlled trails, and a systematic review, was performed mainly in PubMed, Web of Science, and CNKI databases. The main search terms used are as follows: "chronic post-surgical pain", "chronic postoperative pain", "chronic pain", "video assisted thoracic surgery", "thoracic surgery", "risk factor", "pain related". A total of 1,428 articles were searched. Of those, 1,335 irrelevant studies were excluded based on the screening of titles or abstracts. The remaining 93 articles were reviewed in full for eligibility, of which 75 were excluded because they were solely related to the prevalence of CPSP or did not report risk factors for CPSP. Eventually, 18 articles highly correlated with the risk factors for CPSP were included.

Two researchers independently reviewed all the included articles to identify the risk factors for CPSP mentioned in these studies. The preliminary list was tested for readability and feasibility by group members. A new conceptual framework, including ten fields (baseline characteristics, psychological and social factors, health status, primary disease-related, genetic and biological factors, surgery-related, anesthesia management-related, postoperative recovery management, postoperative pain management, primary disease progression and treatment) was preliminarily developed, and an initial item pool containing 58 items was obtained.

Recruitment and panel formation

The panel members were medical professionals from three different grade-A tertiary hospitals and researchers of Guangzhou Pain Society in Guangzhou. The inclusion criteria of consultant experts are as follows: *i*) They should have been engaged in pain management-related medical work for not less than 10 years. However, for specialists in the fields of basic research, if they show academic excellence and have published more than two papers as the first author, the working years may be relaxed appropriately. *ii*) Their professional title should be intermediate or above. *iii*) They should have a bachelor's degree or higher. *iv*) They should be professionals in pain management, including surgeons, anesthetists, pain specialists, nurses, rehabilitation specialists, and pain researchers. Since there is no agreement on the optimal panel size, a carefully considered selection of the most symbolic experts, rather than a large sample, may yield valuable results (*21*). Consequently, we decided to form a majority panel of 24 based on a systematic review (*24*).

Questionnaire development and administration

The research tools were developed with reference to a biopsychosocial approach to postoperative pain and calls for research on the combination of risk factors and pain in clinical settings (*17*). The questionnaires for the two survey rounds were administered in 2021, from September 16th to 24thand October 14th to 24th, respectively.

In Round-1, we introduced the subject to the experts by email and obtained their consent in the questionnaire. The questionnaire was composed of three parts: *i*) general information about the experts: age, working

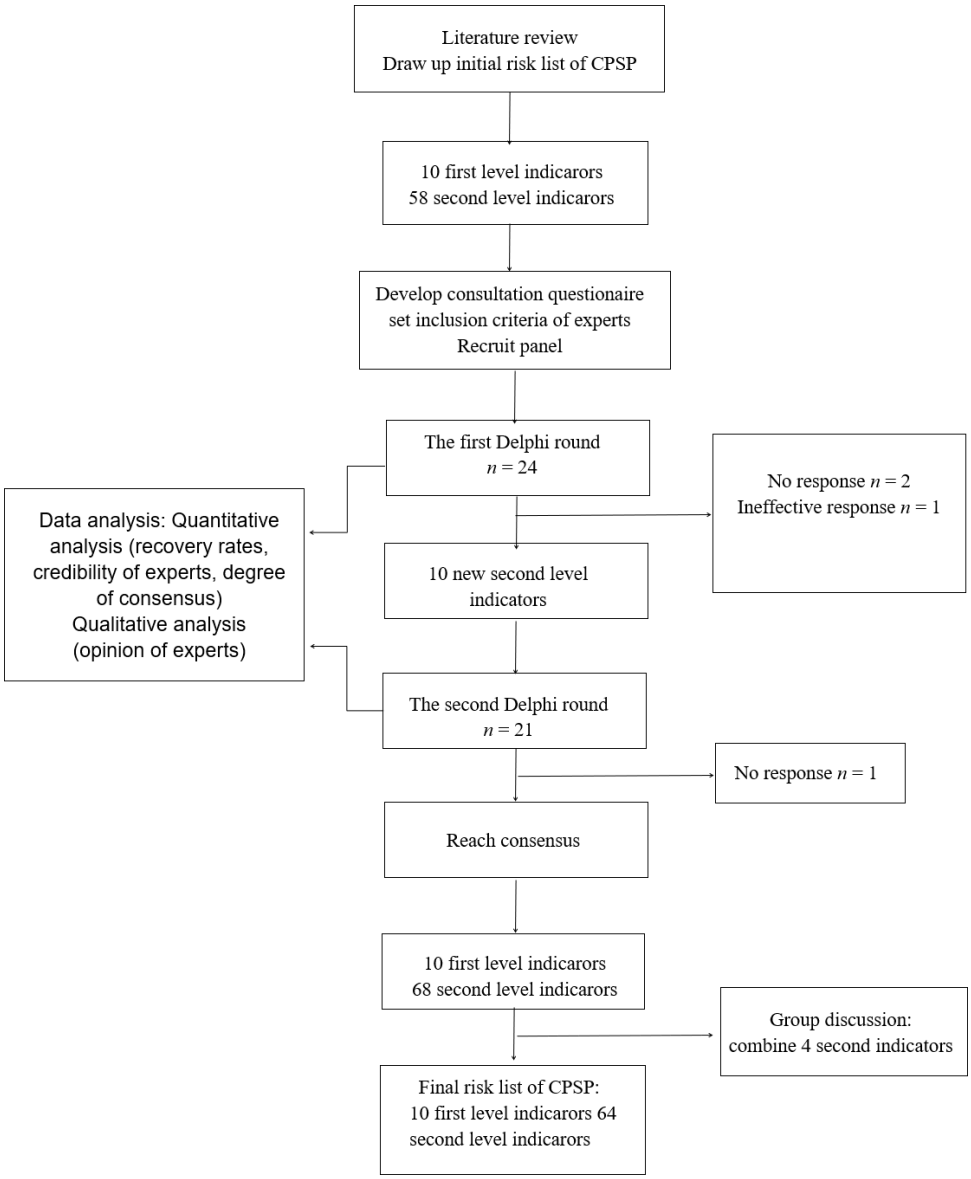


Figure 1. The flowchart of the Delphi process. CPSP, chronic post-surgical pain.

years, educational background, professional title, *etc.*; *ii*) the prediction index system of the CPSP after VATS expert consultation form: the importance and feasibility of the items were evaluated by the way of Likert 5-level scoring method (5 = very important or very good, 4 = important or good, 3 = fair, 2 = unimportant or bad, and 1 = completely unimportant or very bad), and the column for suggestions was provided; *iii*) experts' familiarity with the content of the survey and index judgment. Importance referred to whether these items had a strong correlation with the occurrence of CPSP after VATS. Feasibility referred to whether information could be easily and completely collected from the medical record system. Participants were asked to rank the items based on their theoretical knowledge, evidence from empirical research, clinical experience in pain treatment, and any personal experience. New or missing items were encouraged to be proposed in the first round.

In Round-2, an average score for the importance and feasibility of each item was calculated. The summary results of Round-1 were shared with participants in the form of text prompts. The summary indicated the items that had reached a consensus and those that had not. An improved questionnaire, including the experts' feedback and added items, was sent *via* web-based survey software. At the same time, all the experts had the opportunity to reconsider their evaluations at this turn. After the second round of consultation, our analysis revealed that the results were quite consistent with those of the first round. Therefore, we decided to confirm the prediction index system.

Data analysis

SPSS 26.0 statistical software and online SPSSAU (Statistical Product and Service Software Automatically, a version available on the website) were applied in the data analysis process. After the first round, the

importance and measurability of the indicators were calculated by the form of mean ± standard deviation. The enthusiasm and suggestions of the experts was reflected in the questionnaire return rate and the percentage of suggestions made. Kendall's W and variable coefficients were used to indicate the degree of expert coordination, *i.e.*, whether the experts' scoring results are consistent. The larger the Kendall's W value (value between 0 and 1), the higher the coordination degree of the experts. The significance of the coordination coefficient was analyzed by Chi-square test. The test of significance is a credibility test of the consensus among experts, and $p < 0.05$ was considered statistically significant, indicating the higher the confidence of the results. The variable coefficient presented the coordination degree of the importance and measurability of the items. Generally, an indicator with a variable coefficient < 0.25 is considered a good one. After the second round, we received less dispute about the issue of indicators. According to the importance scoring of each indicator, we analyzed the weighting target using the analytic hierarchy process (AHP). It not only reflects the percentage of a certain factor or indicator, but also emphasizes its relative importance. After discussion in the research group, through analysis and integration, we finally established a risk index system on CPSP after VATS. The test of significance is a credibility test of the consensus among experts, and $p < 0.05$ was considered statistically significant, indicating the higher the confidence of the results.

Results

Sociodemographic and professional characteristics of the expert panel

In the final round, we received a total of 20 valid questionnaires. Fifty-five percent of the participants (11 cases) were male, and forty-five percent (9 cases) were female. They ranged in age from 29 to 65 years old, with a mean age of 45.95 (SD: 8.27) years. Their working years ranged from 6 to 40 years, with an average of 18.5 (SD: 7.67) years. Table 1 presents the sociodemographic and professional characteristics of the Delphi expert panel.

Experts' enthusiasm

In the first round, 24 experts were invited for the questionnaire, and 22 of them responded, with a response rate of 91.67%. Of the 22 collected questionnaires, 1 questionnaire contained so many missing values that it was eliminated, giving a valid questionnaire rate of 95.45% (21/22). In the second round, 21 questionnaires were distributed and 20 of them were returned, with a return rate of 95.23% and a validness rate of 100% (20/20). The suggestion rate (number of experts raising doubts about the items) was 38.10% (8/21) compared to 10.00% (2/20) in the second round (Table 2).

Table 1. Demographic information of the experts

Project	Frequency (*n*)	Proportion (%)
Age (Years)		
< 40	4	20.00
40–50	9	45.00
> 50	7	35.00
Highest degree		
Undergraduate	6	30.00
Master	6	30.00
Doctorate	8	40.00
Work experience (years)		
< 10	2	10.00
10 – 20	12	60.00
> 20	6	30.00
Professional title		
Intermediate level	6	30.00
Senior vice level	7	35.00
Advanced level	7	35.00
Research field		
Thoracic surgeon	3	15.00
Anesthetist	4	20.00
Pain Management specialists	4	20.00
Nurse	4	20.00
Rehabilitation specialist	2	10.00
Basic research specialist in pain	3	15.00

Expert authority coefficient and opinion coordination degree

The judgement coefficient, familiarity coefficient, and authority coefficient were 0.955, 0.793, and 0.966, respectively. When the expert authority coefficient $Cr \geq 0.7$, it demonstrated that the results of the survey were reliable. In the first round of the survey, the Kendall's concordance coefficients for the first- and second-level indicators were 0.397 and 0.366 in importance and 0.288 and 0.255 in measurability, respectively. In the second round, the Kendall's concordance coefficients for the first- and second-level indicators were 0.370 and 0.393 in importance and 0.302 and 0.234 in measurability, respectively. All the Kendall's tests were of statistical significance (all $p < 0.001$) (Table 3).

The first round of Delphi

In the first round, the experts scored the initial draft of the post-VATS CPSP index system containing 58 items in 10 domains. We received 26 suggestions on redefining, adding, merging, and splitting the items. These suggestions were reviewed and the items were integrated in a group discussion, incorporating possible related factors from the literature or expert experience. Ten new items proposed by the experts after modifying were included. Sixteen items were modified, merged or separated. All the retained items and new items entered the second round for the experts to rate. Consequently, a form of 68 items in ten domains was sent to 21 experts for the next round of the survey.

The second round of Delphi

In the second round, no new items were proposed, but the content of the items was further refined. After discussions by our research group, the final form of 64 risk factors in 10 domains was determined (Table 4).

Discussion

After reviewing the literature (*8*) on the basis of our clinical experience, we realized the great diversity of points on the validation, importance, and feasibility of the predisposing risk factors within CPSP, especially after VATS in lung resection (*25*). We retrieved potential and relevant risk factors from systematic review or research, and constructed the initial version of item pool. The modified Delphi method is a rigorous expert consultant, with the assistance of the anonymous panel, rating scale, iteration, and controlled feedback (*21*). The experts were allowed to scale the importance and measurability of the items that have been generated from previous studies, and to propose any items that have an impact on CPSP but have not been mentioned in previous studies. At the same time, we set blanks in the last column of the questionnaire form, where suggestions can be made for adding or deleting any of the items. Through rounds of feedback and statistical analysis, new items could be continuously included, and existing ones could be modified or deleted, to supplement and perfect the item pool, striving to build a comprehensive index system.

The consensus-based set of risk factors provides the first comprehensive understanding of CPSP after VATS. In this study, we applied classical statistical analysis, well known as the Delphi technique. We calculated the means, standard div SD, authority coefficient and Kendall's coefficient of concordance (Kendall's W), which have been widely used and proved effective in previous and similar studies (*26,27*). Hence, we have powerful evidence that this study is scientific, reliable, and trustworthy. Firstly, the valid return rates of both rounds were higher than 90%, indicating that the experts showed great enthusiasm and involvement in each round of consultation. Secondly, the authority coefficient was 0.966, which exceeded the standard value of 0.7, demonstrating that the experts' authority was high and the results were credible. Thirdly, the Kendall's W of the first level in the second round was slightly smaller than that of the first round (0.370 *vs.* 0.397), probably due to their different professional backgrounds and different main focuses, resulting in different views on the attributes of the items. However, the Kendall's W of the second level was higher in Round 2 than in Round 1 (0.393 *vs.* 0.366). Although the Kendall's W did not show the same trend in both rounds, the results were valuable and reliable, showing very good coordination and consistency.

In this study, the experts would qualify each item for attribution and rate the importance and measurability of each item on a scale of 1–5 at each level. The composite index, including biological, psychological and social aspects, is essential to CPSP identification, for the latter is complex and changeable (*28*). At the same time, the biopsychosocial factors were also comprehensive and diverse, so we tried our best to summarize and classify the items. Two experts had doubts about the attribution of the first-level items, but in the second round they reached an agreement on this issue. For the second level of the indicators, some experts — not more than half — held the view that some items did not fit neatly into a particular category. Firstly, there was no standardized classification approach to divide these items/indicators into different dimensions (first-level indicators), and the final categories were largely retrieved from the literature (*12,17,29*) and integrated from our research group's opinions. Secondly, the scope of this item pool was very broad, so the team of experts came from different fields and might have different perspectives. Thirdly, we attempted to make these items easily recognized in a particular way rather than to make them presented.

At the end of the two rounds of consultation,

Table 2. Recovery of the questionnaire and suggestions offered

Questionnaire recovery	First round	Second round
Number of questionnaires distributed	24	21
Number of recycled questionnaires	22	20
Rate of recovery (%)	91.67	95.23
Effective questionnaire	21	20
Effective proportion (%)	95.45	100
Proposed ratio		
Number of experts	8	2
Constituent ratio (%)	38.10	10.00

Table 3. The results of expert opinions' coordination degree

Hierarchical level	The importance				The Measurability			
	Index (*n*)	Kendall's W	x^2	*p*	Index (*n*)	Kendall's W	x^2	*p*
First round								
First-level	10	0.397	74.987	0.000	10	0.288	54.448	0.000
Second-level	58	0.366	438.142	0.000	58	0.255	304.643	0.000
Second round								
First-level	10	0.370	66.599	0.000	10	0.302	54.325	0.000
Second-level	68	0.393	537.245	0.000	68	0.234	314.083	0.000

Table 4. Core risk index system of chronic post-surgical pain after video-assisted thoracic surgery

Index level 1st, 2nd	Importance			Measurability	
	Significance grade	Variable coefficient	Weighting targets	Measurability grade	Variable coefficient
Basic information	3.95 ± 0.69	0.174	0.087	4.90 ± 0.31	0.063
Age	4.40 ± 0.60	0.136	0.119	4.90 ± 0.31	0.063
Gender	4.20 ± 0.70	0.166	0.114	4.90 ± 0.31	0.063
BMI	3.70 ± 0.80	0.217	0.100	4.90 ± 0.31	0.063
Marital status	3.05 ± 1.10	0.360	0.083	4.65 ± 0.59	0.126
Health insurance	2.90 ± 1.12	0.386	0.079	4.70 ± 0.66	0.140
Family member	2.80 ± 1.11	0.395	0.076	4.50 ± 0.76	0.169
Social status	3.30 ± 0.86	0.262	0.089	4.00 ± 1.02	0.256
Educational level	3.30 ± 0.47	0.142	0.089	4.60 ± 0.68	0.148
Psychological and social parameters	4.5 ± 0.51	0.114	0.100	3.95 ± 0.61	0.153
Smoking	3.70 ± 0.86	0.234	0.147	4.65 ± 0.67	0.144
Drinking history	3.60 ± 0.82	0.228	0.143	4.60 ± 0.68	0.148
Sleep distress	4.35 ± 0.67	0.154	0.173	4.40 ± 0.99	0.226
Depression	4.55 ± 0.60	0.133	0.181	4.20 ± 0.83	0.198
Anxiety	4.60 ± 0.60	0.130	0.183	4.20 ± 0.77	0.183
Stress	4.40 ± 0.60	0.136	0.175	3.60 ± 0.88	0.245
Health status and comorbidities	4.65 ± 0.49	0.105	0.103	4.25 ± 0.72	0.169
Operation history	3.95 ± 0.83	0.209	0.113	4.65 ± 0.67	0.144
Hypertension degree	3.15 ± 0.99	0.314	0.090	4.60 ± 0.68	0.148
Diabetes mellitus	3.80 ± 0.95	0.250	0.109	4.60 ± 0.76	0.164
ASA classification	3.60 ± 0.82	0.228	0.103	4.40 ± 0.68	0.155
Emergency operation	3.40 ± 0.88	0.260	0.097	4.60 ± 0.75	0.164
Preoperative pain	4.70 ± 0.73	0.156	0.134	4.65 ± 0.59	0.126
Preoperative sensory assessment	4.35 ± 0.88	0.154	0.127	4.15 ± 0.93	0.225
Respiratory illness	3.55 ± 1.23	0.348	0.102	4.35 ± 0.75	0.171
Primary disease related	4.60 ± 0.68	0.148	0.102	4.65 ± 0.49	0.105
Tumor type and stage	3.75 ± 0.97	0.258	0.187	4.65 ± 0.59	0.126
Tumor progression	4.10 ± 1.02	0.249	0.204	4.45 ± 0.76	0.171
Tumor type	3.35 ± 1.18	0.353	0.167	4.55 ± 0.69	0.151
Preoperative chemotherapy	4.40 ± 0.75	0.171	0.219	4.65 ± 0.76	0.160
Preoperative radiotherapy	4.45 ± 0.76	0.171	0.222	4.75 ± 0.55	0.116
Epigenetic and biological factors	4.00 ± 0.76	0.181	0.889	3.95 ± 0.94	0.239
Genetics	3.20 ± 1.11	0.345	0.284	3.50 ± 1.00	0.286
Inflammatory respond	4.50 ± 0.76	0.169	0.400	4.15 ± 0.81	0.196
Endocrine respond	3.55 ± 1.00	0.281	0.316	4.10 ± 0.79	0.192
Surgery-related	4.80 ± 0.41	0.085	0.106	4.40 ± 0.68	0.155
Surgeon	3.85 ± 0.93	0.242	0.909	4.45 ± 0.89	0.199
Surgical option (VATS / open)	4.65 ± 0.49	0.105	0.109	4.80 ± 0.52	0.109
Operation type	4.15 ± 0.88	0.211	0.097	4.65 ± 0.67	0.144
Operation change	4.40 ± 0.68	0.155	0.103	4.65 ± 0.67	0.144
Surgical site	4.55 ± 0.60	0.133	0.107	4.80 ± 0.41	0.085
VATS type (single-port/three-port)	4.05 ± 0.83	0.204	0.095	4.60 ± 0.75	0.164
Number of chest tube	4.25 ± 0.79	0.185	0.100	4.60 ± 0.68	0.148
Duration of drainage	4.40 ± 0.60	0.136	0.103	4.80 ± 0.52	0.109
Operation time	4.25 ± 0.72	0.169	0.100	4.80 ± 0.52	0.109
Drainage specification	4.10 ± 0.64	0.156	0.096	4.60 ± 0.68	0.148
Anesthesia management-related	4.85 ± 0.37	0.076	0.107	4.75 ± 0.55	0.116
Opioids sum	4.85 ± 0.37	0.076	0.177	4.80 ± 0.41	0.085
NSAIDs sum	4.75 ± 0.44	0.094	0.173	4.80 ± 0.523	0.109
Other kinds of analgesic	4.60 ± 0.50	0.109	0.168	4.75 ± 0.55	0..116
Assisted anesthesia	4.65 ± 0.59	0.126	0.170	4.75 ± 0.44	0.094
Preemptive analgesia	4.65 ± 0.59	0.126	0.169	4.70 ± 0.57	0.122
Intraoperative awareness	3.90 ± 1.12	0.287	0.142	4.00 ± 0.86	0.215
Postoperative recovery management	4.80 ± 0.22	0.045	0.110	4.35 ± 0.67	0.130
Incision healing	4.65 ± 0.59	0.126	0.160	4.70 ± 0.57	0.122
Reconstruction	4.20 ± 0.77	0.183	0.145	4.60 ± 0.68	0.148
Hospital stay	4.05 ± 0.76	0.187	0.140	4.55 ± 0.83	0.181
WBC change	3.65 ± 0.88	0.240	0.126	4.50 ± 0.76	0.169
Drainage of fistula	4.20 ± 0.83	0.198	0.145	4.65 ± 0.59	0.126
Postoperative pleural effusion	3.95 ± 0.89	0.225	0.136	4.45 ± 0.69	0.154
Irritable cough	4.30 ± 0.57	0.133	0.148	4.15 ± 0.88	0.211
Postoperative pain management	4.95 ± 0.22	0.045	0.110	4.60 ± 0.60	0.130
Personal control analgesia (PCA)	4.70 ± 0.57	0.122	0.174	4.60 ± 0.75	0.164
Kinds of analgesic in ward	4.70 ± 0.47	0.100	0.174	4.40 ± 0.94	0.213

Table 4. Core risk index system of chronic post-surgical pain after video-assisted thoracic surgery (continued)

Index level 1st, 2nd	Importance			Measurability	
	Significance grade	Variable coefficient	Weighting targets	Measurability grade	Variable coefficient
Dose of opioids	4.60 ± 0.50	0.109	0.170	4.70 ± 0.47	0.100
Dose of NSAIDs	4.50 ± 0.51	0.114	0.167	4.75 ± 0.44	0.094
Duration of PCA	4.20 ± 0.83	0.198	0.156	4.70 ± 0.66	0.140
Side-effect of analgesic	4.30 ± 0.86	0.201	0.159	4.35 ± 0.75	0.171
Disease progression and treatment	4.05 ± 0.69	0.170	0.090	4.15 ± 0.81	0.196
Tumor recurrence	3.90 ± 1.02	0.262	0.215	4.40 ± 0.75	0.171
Tumor type and stage	3.30 ± 1.08	0.328	0.182	4.45 ± 0.76	0.171
Postoperative chemotherapy	3.80 ± 1.15	0.303	0.209	4.50 ± 0.76	0.169
Postoperative radiotherapy	3.75 ± 1.21	0.322	0.207	4.45 ± 0.83	0.186
Postoperative targeted therapy	3.40 ± 1.10	0.322	0.187	4.45 ± 0.83	0.186

the experts came up with ten new items and several suggestions. One participant believed that how couples get along with each other may affect their medical experience. This item was proposed by a rehabilitation specialist who focused more on involvement and support between couples in the clinical setting. In fact, social support may plays a major role in coping with toxic stimuli, whether physical or mental (*30*). In the second round, another nursing expert noted that this added item was vague and general, and could be covered by the items of marital status and family members. Because this new item was related to the existing ones, we did not include a similar indicator for assessing support from social members. BMI, or body mass index, is the ratio of weight to height, so we decided to remove the item of weight and height. In the category of psychological and social parameters, the dispute centered mainly on which measurement scales were more appropriate for evaluating depression, anxiety, and stress. Previous studies have used the EuroQol 5 Dimensions (EQ5D) questionnaire or the PROMIS questionnaire to assess psychological status (*25,31*). The measurement tool may not be the most appropriate but the simplest and most convenient to use, and this should be made clear in our further research. One expert offered a new perspective on respiratory diseases, including asthma or chronic obstructive pulmonary disease (COPD) and changes in pulmonary function, which would definitely affect the early postoperative respiratory function exercises and slow down the recovery. However, the evidence regarding pain is problematic and needs further investigation. Some experts found that the item of preoperative response to experimentally induced pain was a similar indicator to preoperative sensory assessment and suggested that one of them be retained. Some experts expressed their concerns on chemotherapy, as mentioned in a previous study (*9*), but there are differences in treatment regimens, timing, and side effects, indicating key points for data collection in further research. Despite numerous studies showing that genetic predictors or inflammatory molecules are important evidence (*8,32*), this evidence is not easy to detect and easily routinely tested. It does provide a novel perspective and understanding of genetic testing, inflammatory factors and changes in the internal environment. Larger numbers of studies recommend replacing the conventional thoracic drainage tube with a new ultrafine chest tube (central venous catheter), which has proved to reduce postoperative pain (*33*). The experts proposed that both the duration and the specifications of drainage also play a role in postoperative pain, and are worth emphasizing. The use of parecoxib sodium for preemptive analgesia has become a hot topic with the expectation of reducing the pain score and even reducing opioid consumption (*34*). The experts pointed out that the efficacy of parecoxib for preemptive analgesia may be controversial, but its benefits are still noteworthy. At the same time, they considered that the experience of intraoperative consciousness, though rare, is potentially catastrophic. Patients can recall the misery of surgical pain, which can bring about follow-up psychological problems. Research has been focused on the importance of the prolonged drainage, uniport VATS, and time of operation for CPSP (*12*), but less on the complications of drainage fistulas and pleural effusions. We also adopted the idea that postoperative bad cough might induce serious pain. Multiple analgesic management will bring various side effects, such as postoperative nausea and vomiting, at which time the nurse would withdraw the patient-controlled analgesia, so the pain is not relieved (*7*). Targeted therapy is one of the treatments for malignant diseases, and the experts suggested in the questionnaire that people can suffer from weakened immunity, which would induce pain, but the mechanism remains unclear and still needs attention.

The overall domains have been identified and specific items have been developed after the two rounds of consultation. The risk factor system in this study is relatively comprehensive and multi-dimensional. However, attention must be paid to the wording, splitting or integration of the items, as well as to further guidance and scope of application. In short, while some indicators may be very useful, others may need to be adapted. The list of indicators is in accordance with the guidelines or other recommended perioperative management

strategies for patients undergoing lung surgery, with the best availability and high levels of evidence (*35*). The index system will provide an important resource for clinical practitioners and holds great promise for early identification of patients at a high risk of CPSP after VATS.

In this study, we invited experts from different fields, and summarized the suggestions from different and unique perspectives. In addition, we included prior evidence that is based on systematic and prospective studies of CPSP. Hence, the index system combines the strengths of being empirical and experimental. Delphi evaluations are typically less expensive than more traditional forms of data collection, such as surveys and interviews. Since the heterogeneous results of CPSP highlight the current challenges in identifying risk factors, our study has the potential to represent a valuable contribution and a meaningful guideline, thus pointing the way for further research.

However, our study is limited to regional expert consultants from several Guangzhou grade-A tertiary hospitals, and their opinions do not represent the whole world. But the literature comes from articles published worldwide, which can compensate for this shortcoming. Another limitation is that all the risk factors were grouped into biological, psychological, and social domains throughout the perioperative period. Some risk factors could have fit into other categories, and different categorizations may lead to different interpretations of the items. Additionally, the Delphi process is highly dependent on the expertise of each panelist and their ability to make unbiased and accurate judgments. The results can be difficult to replicate if another group of experts evaluates the same issue.

Conclusions

This index system provides a consensus-based resource for clinicians and researchers seeking help for patients at a high risk of CPSP after VATS. Increased clinical awareness and a full understanding of how to screen and identify people with CPSP problems may lead to earlier recognition of chronic pain and greater facilitation of professional prevention. We developed the first version of the risk index for the detection of patients at high risk of CPSP after VATS for lung resection in a modified Delphi method. The development of the index system was informed by a biopsychosocial approach to postoperative pain and by calls for research on combining risk factors with pain in clinical settings. The item pool, where the items were strictly selected using the Delphi technique, is highly recommended. Researchers are welcome to refer to the list of indicators, especially those with high scores in importance and measurability.

Funding: This project was supported by a grant from the Institute of Science and Technology of the National Health Commission (2021KYSHX01505) and the National Key R&D Program of China (2018YFC2001805).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022; 72:7-33.
2. Zheng RS, Zhang SW, Sun KX, Chen R, Wang SM, Li L, Zeng HM, Wei WW, He J. Cancer statistics in China, 2016. Zhonghua Zhong Liu Za Zhi. 2023; 45:212-220. (in Chinese)
3. Sihoe ADL. Video-assisted thoracoscopic surgery as the gold standard for lung cancer surgery. Respirology. 2020; 25 (Suppl 2):49-60.
4. Niraj G, Kelkar A, Kaushik V, Tang Y, Fleet D, Tait F, McMillan T, Rathinam S. Audit of postoperative pain management after open thoracotomy and the incidence of chronic postthoracotomy pain in more than 500 patients at a tertiary center. J Clin Anesth. 2017; 36:174-177.
5. Takenaka S, Saeki A, Sukenaga N, Ueki R, Kariya N, Tatara T, Hirose M. Acute and chronic neuropathic pain profiles after video-assisted thoracic surgery: A prospective study. Medicine (Baltimore). 2020; 99:e19629.
6. Bayman EO, Parekh KR, Keech J, Selte A, Brennan TJ. A prospective study of chronic pain after thoracic surgery. Anesthesiology. 2017; 126:938-951.
7. Feray S, Lubach J, Joshi GP, Bonnet F, Van de Velde M, Anaesthesia PWGotESoR, Pain T. PROSPECT guidelines for video-assisted thoracoscopic surgery: A systematic review and procedure-specific postoperative pain management recommendations. Anaesthesia. 2022; 77:311-325.
8. Fregoso G, Wang A, Tseng K, Wang J. Transition from acute to chronic pain: Evaluating risk for chronic postsurgical pain. Pain Physician. 2019; 22:479-488.
9. Clephas PRD, Hoeks SE, Trivella M, Guay CS, Singh PM, Klimek M, Heesen M. Prognostic factors for chronic post-surgical pain after lung or pleural surgery: A protocol for a systematic review and meta-analysis. BMJ Open. 2021; 11:e051554.
10. Schug SA, Lavand'homme P, Barke A, Korwisi B, Rief W, Treede RD; IASP Taskforce for the Classification of Chronic Pain. The IASP classification of chronic pain for ICD-11: Chronic postsurgical or posttraumatic pain. Pain. 2019; 160:45-52.
11. Fiorelli S, Cioffi L, Menna C, Ibrahim M, De Blasi RA, Rendina EA, Rocco M, Massullo D. Chronic pain after lung resection: Risk factors, neuropathic pain, and quality of life. J Pain Symptom Manage. 2020; 60:326-335.
12. Tong Y, Wei P, Wang S, Sun Q, Cui Y, Ning N, Chen S, He X. Characteristics of postoperative pain after VATS and pain-related factors: The experience in National Cancer Center of China. J Pain Res. 2020; 13:1861-1867.
13. Althaus A, Hinrichs-Rocker A, Chapman R, Arranz Becker O, Lefering R, Simanski C, Weber F, Moser KH, Joppich R, Trojan S, Gutzeit N, Neugebauer E. Development of a risk index for the prediction of chronic post-surgical pain. Eur J Pain. 2012; 16:901-910.
14. Kar P, Sudheshna KD, Padmaja D, Pathy A, Gopinath R.

Chronic pain following thoracotomy for lung surgeries: It's risk factors, prevalence, and impact on quality of life - A retrospective study. Indian J Anaesth. 2019; 63:368-374.
15. VanDenKerkhof EG, Peters ML, Bruce J. Chronic pain after surgery: time for standardization? A framework to establish core risk factor and outcome domains for epidemiological studies. Clin J Pain. 2013; 29:2-8.
16. Kraychete DC, Sakata RK, Lannes Lde O, Bandeira ID, Sadatsune EJ. Postoperative persistent chronic pain: What do we know about prevention, risk factors, and treatment. Braz J Anesthesiol. 2016; 66:505-512.
17. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: Risk factors and prevention. Lancet. 2006; 367:1618-1625.
18. Niederberger M, Koberich S, members of the DeWiss N. Coming to consensus: The Delphi technique. Eur J Cardiovasc Nurs. 2021; 20:692-695.
19. Hsu CC, Sandford BA. The Delphi technique: Making sense of consensus. Practical assessment, research, and evaluation. 2007; 12:10.
20. Rowe G, Wright G. The Delphi technique as a forecasting tool: Issues and analysis. Int J Forecast. 1999; 15:353-375.
21. Drumm S, Bradley C, Moriarty F. 'More of an art than a science'? The development, design and mechanics of the Delphi Technique. Res Social Adm Pharm. 2022; 18:2230-2236.
22. Sinha IP, Smyth RL, Williamson PR. Using the Delphi technique to determine which outcomes to measure in clinical trials: Recommendations for the future based on a systematic review of existing studies. PLoS Med. 2011; 8:e1000393.
23. Junger S, Payne SA, Brine J, Radbruch L, Brearley SG. Guidance on Conducting and REporting DElphi Studies (CREDES) in palliative care: Recommendations based on a methodological systematic review. Palliat Med. 2017; 31:684-706.
24. Diamond IR, Grant RC, Feldman BM, Pencharz PB, Ling SC, Moore AM, Wales PW. Defining consensus: A systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol. 2014; 67:401-409.
25. Bayman EO, Parekh KR, Keech J, Larson N, Vander Weg M, Brennan TJ. Preoperative patient expectations of postoperative pain are associated with moderate to severe acute pain after VATS. Pain Med. 2019; 20:543-554.
26. Cui K, Shen F, Han B, Liu H, Chen J. Establishment and application of an index system for prevention of coal workers' pneumoconiosis: ADelphi and analytic hierarchy process study in four state-owned coal enterprises of China. Occup Environ Med. 2018; 75:654-660.
27. Chen L, Wu Y, Wang S, Zhao H, Zhou C. Construction of evidence-based practice competencies for nurses in China: A modified Delphi study. Nurse Educ Today. 2021; 102:104927.
28. Li Q, Dai W, Chen X, Su D, Yu W, Gu X. Publication trends and hot spots in chronic postsurgical pain (CPSP) research: A 10-year bibliometric analysis. J Pain Res. 2021; 14:2239-2247.
29. Brunelli A, Gooseman MR, Pompili C. Evaluation of risk for thoracic surgery. Surg Oncol Clin N Am. 2020; 29:497-508.
30. Katz J, Pagé MG, Weinrib A, Clarke H. Identification of risk and protective factors in the transition from acute to chronic post surgical pain. Clinical pain management: A practical guide (Mary E. Lynch, Kenneth D. Craig OC, Philip W. Peng, eds.). John Wiley & Sons Ltd. New Jersey, USA. 2022; pp. 50-59.
31. Bendixen M, Jørgensen OD, Kronborg C, Andersen C, Licht PB. Postoperative pain and quality of life after lobectomy *via* video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: A randomised controlled trial. Lancet Oncology. 2016; 17:836-844.
32. Montes A, Roca G, Sabate S, Lao JI, Navarro A, Cantillo J, Canet J; GENDOLCAT Study Group. Genetic and clinical factors associated with chronic postsurgical pain after hernia repair, hysterectomy, and thoracotomy: A two-year multicenter cohort study. Anesthesiology. 2015; 122:1123-1141.
33. Song Y, Zheng C, Zhou S, Cui H, Wang J, Wang J, Wang W, Liu L, Liu J. The application analysis of 8F ultrafine chest drainage tube for thoracoscopic lobectomy of lung cancer. J Cardiothorac Surg. 2021; 16:104.
34. Ling YH, Tai YH, Wu HL, Fu WL, Tsou MY, Chang KY. Evaluating the association of preoperative parecoxib with acute pain trajectories after video-assisted thoracoscopic surgery: A single-centre cohort study in Taiwan. BMJ Open. 2021; 11:e038985.
35. Batchelor TJP, Rasburn NJ, Abdelnour-Berchtold E, Brunelli A, Cerfolio RJ, Gonzalez M, Ljungqvist O, Petersen RH, Popescu WM, Slinger PD, Naidu B. Guidelines for enhanced recovery after lung surgery: Recommendations of the Enhanced Recovery After Surgery (ERAS®) Society and the European Society of Thoracic Surgeons (ESTS). Eur J Cardiothorac Surg. 2019; 55:91-115.

Received April 23, 2023; Revised May 24, 2023; Accepted June 11, 2023.

Released online in J-STAGE as advance publication August 10, 2023.

**Address correspondence to*:
Haihua Shu, Department of Anesthesiology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, 106 Zhongshan Second Road, Yuexiu District, Guangzhou 510080, Guangdong, China.
E-mail: shuhaihua@hotmail.com

Global Health & Medicine. 2023; 5(4):238-245.
BRIEF REPORT
DOI: 10.35772/ghm.2023.01001

Economic burden of cancer attributable to modifiable risk factors in Japan

Eiko Saito[1,*], Shiori Tanaka[2], Sarah Krull Abe[2], Mayo Hirayabashi[2], Junko Ishihara[3], Kota Katanoda[4], Yingsong Lin[5], Chisato Nagata[6], Norie Sawada[7], Ribeka Takachi[8], Atsushi Goto[9], Junko Tanaka[10], Kayo Ueda[11], Megumi Hori[12], Tomohiro Matsuda[13], Manami Inoue[2]

[1] Institute for Global Health Policy Research, Bureau of International Health Cooperation, National Center for Global Health and Medicine, Tokyo, Japan;
[2] Division of Prevention, Institute for Cancer Control, National Cancer Center, Tokyo, Japan;
[3] School of Life and Environmental Science, Department of Food and Life Science, Azabu University, Kanagawa, Japan;
[4] Division of Surveillance and Policy Evaluation, National Cancer Center Institute for Cancer Control, Tokyo, Japan;
[5] Department of Public Health, Aichi Medical University School of Medicine, Nagakute, Japan;
[6] Department of Epidemiology and Preventive Medicine, Gifu University Graduate School of Medicine, Gifu, Japan;
[7] Division of Cohort Research, Institute for Cancer Control, National Cancer Center, Tokyo, Japan;
[8] Department of Food Science and Nutrition, Graduate School of Humanities and Sciences, Nara Women's University, Nara, Japan;
[9] Yokohama City University, Department of Health Data Science, Graduate School of Data Science, Yokohama, Japan;
[10] Department of Epidemiology, Infectious Disease Control and Prevention, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan;
[11] Department of Environmental Engineering, Graduate School of Engineering, Kyoto University, Kyoto, Japan;
[12] School of Nursing, University of Shizuoka, Shizuoka, Japan;
[13] Division of International Health Policy Research, Institute for Cancer Control, National Cancer Center, Tokyo, Japan.

Abstract: Controlling avoidable causes of cancer may save cancer-related healthcare costs and indirect costs of premature deaths and productivity loss. This study aimed to estimate the economic burden of cancer attributable to major lifestyle and environmental risk factors in Japan in 2015. We evaluated the economic cost of cancer attributable to modifiable risk factors from a societal perspective. We obtained the direct medical costs for 2015 from the National Database of Health Insurance Claims and Specific Health Checkups of Japan, and estimated the indirect costs of premature mortality and of morbidity due to cancer using the relevant national surveys in Japan. Finally, we estimated the economic cost of cancer associated with lifestyle and environmental risk factors. The estimated cost of cancer attributable to lifestyle and environmental factors was 1,024,006 million Japanese yen (¥) (8,460 million US dollars [$]) for both sexes, and ¥673,780 million ($5,566 million) in men and ¥350,226 million ($2,893 million) in women, using the average exchange rate in 2015 ($1 = ¥121.044). A total of ¥285,150 million ($2,356 million) was lost due to premature death in Japan in 2015. Indirect morbidity costs that could have been prevented were estimated to be ¥200,602 million ($1,657 million). Productivity loss was highest for stomach cancer in men (¥28,735 million/$237 million) and cervical cancer in women (¥24,448 million/$202 million). Preventing and controlling cancers caused by infections including *Helicobacter pylori*, human papillomavirus and tobacco smoking will not only be life-saving but may also be cost-saving in the long run.

***Keywords*:** cost of illness, economic burden, cancer, population attributable fraction

Introduction

Cancer is a major public health issue, and has also been the leading cause of death in Japan since 1981 (*1*). Around 378,000 people died from cancer in 2020, and 999,000 cancer cases were newly diagnosed in 2019 (*2*). Recent statistics suggest that one in two Japanese people will be diagnosed with cancer during their lifetime (*2*). There is also wide agreement that many cancers are caused by lifestyle and environmental risk factors, which can be prevented if appropriate measures are taken (*3*).

The proportion of cancers that are associated with certain risk factors, such as lifestyle and environmental factors, is often referred to as the population attributable fraction (PAF). PAF is defined as the fraction of cancer attributable to a particular exposure that could be averted if the exposure were reduced to a theoretically minimal level. To date, several comprehensive assessments of the

PAF of cancer have been reported in western countries *(4-6)* and in Asia (*7*). Further, updated findings on the disease burden of cancer associated with preventable risk factors in Japan were reported in 2022 (*8*), providing the PAF of major lifestyle and environmental risk factors.

Despite mounting evidence on disease burden, however, only a few studies have evaluated the economic burden cancer poses on society (*9-12*). According to the Estimates of National Medical Care Expenditure in fiscal year 2015, the direct medical and non-medical costs of all diseases amounted to 30,046 billion Japanese yen (248 billion US dollars as of 2015), of which cancer-related costs constituted 12% (*13*). Beyond direct costs, cancer incurs a heavy economic burden due to premature deaths, temporary work cessation during treatment, and permanent exit from the workforce. Preventing causes of cancer may save cancer-related healthcare costs and indirect costs of premature death and productivity loss. Hence, quantification of the avoidable costs of cancer is important in identifying the financial impact of cancer control policies.

Here, we aimed to estimate the economic burden of cancer attributable to major lifestyle and environmental risk factors using the latest data on population attributable fractions in Japan.

Materials and Methods

We evaluated the economic cost of cancer attributable to modifiable risk factors based on the prevalence-based cost-of-illness approach (*14*). We adopted a societal perspective for our analysis, which included direct healthcare costs, indirect morbidity costs and indirect mortality costs due to lifestyle and environmental risk factors.

Data sources

We obtained the number of cancer patients who received any type of healthcare service and the associated direct medical costs for 2015 from the aggregated datasets of the National Database of Health Insurance Claims and Specific Health Checkups of Japan (the NDB Japan) by the Ministry of Health, Labour and Welfare, which covers 99.9% of hospital or medical clinic claims nationwide. Details of the NDB Japan data can be found elsewhere (*15,16*). We classified sex- and age-specific number of patients and associated costs in 2015 by 20 cancer sites reported as the principal diagnosis according to the WHO International Classification of Diseases, 10th Revision (ICD-10) diagnosis codes. The list of ICD-10 codes used in the current study is shown in Table 1. Because the NDB data and other public statistics were obtained in an aggregated format, ethical approval for this study was not necessary.

The most up-to-date data on population attributable fraction (PAF) of cancer due to lifestyle and environmental risk factors in Japan is for 2015 (*8*), namely tobacco smoking (both active and passive) (*17*), alcohol drinking (*18*), excess bodyweight (*19*), physical inactivity (*19*), infectious agents (*Helicobacter pylori [H. pylori]*, hepatitis C virus, hepatitis B virus, human papillomavirus [HPV], Epstein-Barr virus, and human T-cell leukemia virus type 1) (*20*), dietary intake (highly salted food (*21*), fruit, vegetables, dietary fiber (*22*), red and processed meat (*23*)), exogenous hormone use (*24*), never breastfeeding (*25*) and air pollution (*26*). All of the aforementioned factors are considered potentially modifiable *via* environmental policy, lifestyle change, population-based screening or through vaccination programs.

Direct medical costs

Direct medical costs denote the cost of resources consumed for treatment of the disease, and includes all costs of healthcare and medical examinations during hospitalization and outpatient visits, prescriptions and drugs. The cost of each cancer site attributable to modifiable risk factors was calculated using the following equation (*27*).

$$\text{Attributable cost of cancer } i = \sum \text{PAF}_{ijk} \times \text{THC}_{ijk}$$

where:

Attributable cost of cancer i = direct medical costs of cancer site i attributable to lifestyle and environmental risk factors, including inpatient hospitalizations, outpatient visits, prescriptions and drugs

PAF_{ijk} = PAF of cancer incidence i due to lifestyle and environmental risk factors among people in 5-year age group j by gender k

THC_{ijk} = total direct medical costs for treating cancer i among people in age group j by gender k

Table 1 lists site-specific data on the number of patients extrapolated from the NDB Japan. A total of 2.1 million men and 1.9 million women received cancer treatment in 2015.

Indirect mortality costs

We also estimated the economic cost of potential work-life lost due to premature deaths from cancer, which are attributable to modifiable risk factors. Indirect mortality costs attributable to lifestyle and environmental risk factors were calculated by the net present value of future productivity using the following equation (*27*) :

$$\text{Indirect mortality cost of cancer } i = \sum \text{PAF}_{ijk} \times \text{NDEATH}_{ijk} \times \text{PVLE}_{jk} \times \text{EMP}_{jk}$$

where:

Indirect mortality cost of cancer i = indirect mortality costs from productivity losses due to premature deaths from cancer site i that are attributable to lifestyle and

Table 1. Number of cancer patients by cancer site in Japan, 2015

Cancer site	ICD-10	Number of patients
Both sexes, all cancers	C00-C97	4,045,940
Men		
All cancers	C00-C97	2,107,331
Prostate	C61	551,195
Stomach	C16	316,112
Colon	C18	230,125
Lung, trachea	C33-C34	211,306
Bladder	C67	146,038
Rectum	C19-C20	122,297
Liver	C22	75,478
Kidney and other urinary organs	C64-C66 C68	73,708
Malignant lymphoma	C81-C85 C96	69,500
Esophagus	C15	67,276
Oral cavity and pharynx	C00-C14	47,589
Pancreas	C25	37,090
Leukemia	C91-C95	34,314
Gallbladder and bile ducts	C23-C24	27,351
Larynx	C32	26,669
Women		
All cancers	C00-C97	1,938,609
Breast	C50	659,970
Colon	C18	197,745
Stomach	C16	154,807
Lung, trachea	C33-C34	134,500
Corpus uteri	C54	79,055
Rectum	C19-C20	74,965
Cervix uteri	C53	73,972
Malignant lymphoma	C81-C85 C96	67,830
Ovary	C56	60,852
Bladder	C67	41,767
Liver	C22	36,636
Kidney and other urinary organs	C64-C66 C68	35,338
Pancreas	C25	33,146
Leukemia	C91-C95	28,457
Gallbladder and bile ducts	C23-C24	22,383
Oral cavity and pharynx	C00-C14	19,267
Esophagus	C15	14,707
Larynx	C32	2,163

environmental risk factors

PAF_{ijk} = PAF of cancer mortality *i* due to lifestyle and environmental risk factors among people in 5-year age group *j* by gender *k*

$NDEATH_{ijk}$ = number of deaths from cancer site *i* among people in age group *j* by gender *k*

$PVLE_{jk}$ = present value of potential lifetime earnings in age group j by gender k discounted at an annual rate of 3%

EMP_{jk} = average employment rate among people in age group *j* by gender *k*

The number of cancer deaths during 2015 by cancer site, 5-year age group, and gender were obtained from the Cancer Statistics available on the Cancer Information Service website (*2*). This was then used to derive the remaining years of working life by subtracting the age at death from the retirement age of 65 years. Subsequently, we multiplied the remaining years of working life by the average annual income for the 5-year age group reported in the Basic Survey on Wage Structure 2015 (*28*) and adjusted the future earnings lost to the present values with a discount rate of 3% according to the WHO guide to cost-effectiveness (*29*).

Indirect morbidity costs

We estimated the indirect costs of cancer following the human capital approach (*30*). The indirect costs of cancer in this study denote the economic value of productivity loss associated with absenteeism due to hospitalization and receipt of healthcare treatment. The costs of indirect morbidity costs attributable to modifiable risk factors were calculated using the following equation (*27*).

$$\text{Indirect morbidity cost of cancer } i = \sum \text{PAF}_{ijk} \times \text{TWLD}_{ijk} \times \text{ADW}_{j} \times \text{EMP}_{jk}$$

where:

Indirect morbidity cost of cancer *i* = indirect morbidity costs from productivity losses due to cancer site *i* that are attributable to lifestyle and environmental risk factors

PAF_{ijk} = PAF of cancer incidence *i* due to lifestyle and environmental risk factors among people in 5-year age group *j* by gender *k*

$TWLD_{ijk}$ = total annual work-loss days due to hospitalization and outpatient visits for cancer site *i* among people in age group *j* by gender *k*

ADW_j = average daily wage among people in age group j

EMP_{jk} = average employment rate among people in age group *j* by gender *k*

We estimated the indirect morbidity cost of cancer attributable to modifiable risk factors by multiplying the total number of work-loss days among patients aged 20 to 65 years by the average daily income and adjusted by the average employment rates of the corresponding age group. The number of work-loss days was estimated by multiplying the annual hospitalization days and outpatient visits for each cancer site reported in the Patient Survey 2014 (*31*) by the age-, gender- and site-specific number of patients. We estimated the average daily wage for the 5-year age group from the Basic Survey on Wage Structure 2015 (*28*). The average employment rates by gender and 5-year age group were obtained from the Labour Force Survey 2015 (*32*).

Further, we performed disaggregated estimation of the total economic costs of cancer by major five modifiable risk factors, namely active tobacco smoking (PAF: 15.2% of all cancer incidence), alcohol drinking (PAF: 6.2%), infectious agents (*H. pylori*, hepatitis C virus, hepatitis B virus, HPV, Epstein-Barr virus, and human T-cell leukemia virus type) (PAF: 16.6%), excess bodyweight (PAF: 0.7%), and physical inactivity (PAF: 1.3%) (*8*). These risk factors could be avoided if the exposure were either eliminated or reduced to the theoretical minimum risk exposure distribution. In this study, all the economic costs are presented in 2015 prices in Japanese yen (JPY), which was converted to US

dollars (USD) using the annual average exchange rate of the same year (1 USD = 121.044 yen).

Results and Discussion

Total economic costs of cancer

In 2015, the total number of cancer patients who received any type of healthcare service and were reported to the NDB Japan was 4,045,940 persons (men, 2,107,331 persons; women, 1,938,609 persons). Prostate was the most common cancer site in men (551,195 persons), followed by stomach (316,112 persons) and colon (230,125 persons). In women, breast was the most common cancer site (659,970 persons), followed by colon (197,745 persons) and stomach (154,807 persons). Population attributable fraction of cancer incidence was highest in stomach cancer in men (85.05%) and cervical cancer in women (100%) (*8*).

Table 2 lists the total economic costs and associated cost components of cancer as of 2015. The overall estimated cost of cancer inclusive of direct medical costs, indirect mortality costs and indirect morbidity costs was ¥2,859,727 million ($23,626 million) for both sexes, ¥1,494,581 million ($12,347 million) in men, and ¥1,365,146 million ($11,278 million) in women. The direct medical costs of cancer, which include all costs of healthcare and medical examinations during hospitalization and outpatient visits, and prescriptions and drugs were highest in male prostate cancer (¥189,723 million /$1,567 million), and breast cancer in women (¥200,249 million/$1,654 million).

Table 2 also summarizes the economic cost of potential work-life lost due to premature deaths from cancer, with a cut-off age of 65 (age of retirement in Japan). A total of ¥726,943 million ($6,006 million) was estimated to be lost due to premature death in Japan in 2015. Lung cancer incurred the highest indirect mortality

Table 2. Total economic costs of cancer by cancer site, Japan, 2015

Cancer Site	Direct medical costs*		Indirect mortality costs*		Indirect morbidity costs*		Total costs*	
	JPY	USD	JPY	USD	JPY	USD	JPY	USD
Both sexes, all cancers	1,520,487	12,561	726,943	6,006	612,297	5,058	2,859,727	23,626
Men								
All cancers	848,537	7,010	393,309	3,249	252,736	2,088	1,494,581	12,347
Stomach	79,565	657	49,565	409	33,794	279	162,923	1,346
Lung, trachea	101,021	835	68,795	568	23,303	193	193,118	1,595
Colon	76,649	633	37,361	309	29,233	242	143,243	1,183
Liver	34,089	282	30,573	253	8,679	72	73,341	606
Leukemia	45,636	377	20,782	172	12,738	105	79,156	654
Rectum	52,361	433	27,884	230	20,919	173	101,165	836
Esophagus	20,837	172	16,845	139	8,512	70	46,194	382
Bladder	25,655	212	4,422	37	12,756	105	42,833	354
Oral cavity and pharynx	15,985	132	14,960	124	11,835	98	42,780	353
Kidney and other urinary organs	21,925	181	9,712	80	13,524	112	45,161	373
Pancreas	24,510	202	33,786	279	5,565	46	63,861	528
Larynx	5,543	46	660	5	3,283	27	9,486	78
Prostate	189,723	1,567	2,312	19	19,051	157	211,087	1,744
Malignant lymphoma	33,136	274	14,394	119	16,930	140	64,459	533
Gallbladder and bile ducts	10,846	90	8,421	70	4,085	34	23,353	193
Women								
All cancers	671,950	5,551	333,634	2,756	359,561	2,971	1,365,146	11,278
Stomach	38,100	315	28,389	235	16,136	133	82,625	683
Breast	200,249	1,654	86,107	711	146,491	1,210	432,846	3,576
Lung, trachea	62,664	518	22,299	184	13,261	110	98,224	811
Liver	17,418	144	5,222	43	2,027	17	24,667	204
Cervix uteri	9,936	82	29,593	244	24,448	202	63,977	529
Colon	61,993	512	25,644	212	18,919	156	106,557	880
Leukemia	28,358	234	10,770	89	8,709	72	47,837	395
Rectum	27,082	224	11,606	96	10,539	87	49,227	407
Corpus uteri	12,330	102	9,602	79	16,736	138	38,669	319
Esophagus	4,600	38	4,188	35	1,651	14	10,440	86
Pancreas	20,453	169	14,657	121	3,130	26	38,239	316
Malignant lymphoma	27,281	225	6,656	55	12,353	102	46,290	382
Oral cavity and pharynx	4,885	40	4,872	40	3,663	30	13,420	111
Bladder	6,903	57	1,425	12	2,744	23	11,072	91
Kidney and other urinary organs	9,247	76	2,467	20	4,249	35	15,962	132
Ovary	18,528	153	27,826	230	14,277	118	60,631	501
Gallbladder and bile ducts	8,957	74	4,432	37	1,488	12	14,877	123
Larynx	386	3	114	1	338	3	838	7

*Data are millions of Japanese yen (JPY) and US dollars (USD).

cost in men (¥68,795 million/$568 million). In women, breast cancer caused the highest cost of indirect mortality (¥86,107 million/$711 million). The indirect morbidity costs, which means the annual productivity loss due to the absenteeism associated with cancer treatment, was estimated at ¥612,297 million/$5,058 million in 2015. The type of cancer that incurred the greatest productivity loss in men was stomach cancer (¥33,794 million/$279 million). In women, the highest productivity loss was seen in breast cancer (¥146,691 million/$1,210 million).

Economic costs of cancer attributable to modifiable risk factors

Table 3 lists the cost components of economic costs attributable to modifiable risk factors of cancer. The overall estimated cost of cancer inclusive of direct medical costs, indirect mortality costs and indirect morbidity costs that were attributable to lifestyle and environmental factors was ¥1,024,006 million ($8,460 million) for both sexes, ¥673,780 million ($5,566 million) in men, and ¥350,226 million ($2,893 million) in women. The direct medical costs of cancer associated with modifiable risk factors were highest in stomach cancer in both men (¥67,655 million /$559 million) and women (¥33,187 million/$274 million).

Table 3 also shows the indirect cost of mortality from cancer due to modifiable risk factors. A total of ¥285,150 million ($2,356 million) was lost due to premature death in Japan in 2015 which could have been potentially averted. Lung cancer incurred the highest indirect mortality cost in men (¥45,132 million/$373 million) and cervical cancer in women (¥29,593 million/$244 million). Similarly, the estimated indirect morbidity costs that could have been theoretically prevented were ¥200,602 million ($1,657 million) in 2015. Modifiable productivity loss was the highest in stomach cancer in men (¥28,735 million/$237 million), and cervical cancer

Table 3. Total economic costs attributable to modifiable risk factors, Japan, 2015

Cancer Site	Direct medical costs*		Indirect mortality costs*		Indirect morbidity costs*		Total costs*	
	JPY	USD	JPY	USD	JPY	USD	JPY	USD
Both sexes, all cancers	538,254	4,447	285,150	2,356	200,602	1,657	1,024,006	8,460
Men								
All cancers	368,460	3,044	195,574	1,616	109,746	907	673,780	5,566
Stomach	67,655	559	42,930	355	28,735	237	139,320	1,151
Lung, trachea	67,025	554	45,132	373	15,461	128	127,618	1,054
Colon	32,221	266	15,222	126	12,289	102	59,731	493
Liver	25,317	209	23,033	190	6,446	53	54,796	453
Leukemia	17,904	148	6,544	54	4,998	41	29,445	243
Rectum	17,871	148	9,267	77	7,140	59	34,278	283
Esophagus	17,163	142	13,718	113	7,011	58	37,893	313
Bladder	10,680	88	1,801	15	5,310	44	17,791	147
Oral cavity and pharynx	10,011	83	9,139	76	7,412	61	26,562	219
Kidney and other urinary organs	8,512	70	4,148	34	5,250	43	17,910	148
Pancreas	6,580	54	9,017	74	1,494	12	17,091	141
Larynx	4,268	35	498	4	2,528	21	7,294	60
Prostate	2,621	22	69	1	263	2	2,953	24
Malignant lymphoma	2,178	18	668	6	1,113	9	3,959	33
Gallbladder and bile ducts	332	3	226	2	125	1	684	6
Women								
All cancers	169,793	1,403	89,576	740	90,857	751	350,226	2,893
Stomach	33,187	274	25,570	211	14,055	116	72,812	602
Breast	27,992	231	12,190	101	20,477	169	60,658	501
Lung, trachea	20,820	172	6,962	58	4,406	36	32,188	266
Liver	12,199	101	3,793	31	1,419	12	17,411	144
Cervix uteri	9,936	82	29,593	244	24,448	202	63,977	529
Colon	9,382	78	3,870	32	2,863	24	16,116	133
Leukemia	8,242	68	2,723	22	2,531	21	13,495	111
Rectum	2,640	22	1,023	8	1,028	8	4,691	39
Corpus uteri	1,984	16	1,782	15	2,693	22	6,458	53
Esophagus	1,975	16	1,682	14	709	6	4,366	36
Pancreas	1,568	13	1,060	9	240	2	2,868	24
Malignant lymphoma	1,565	13	291	2	708	6	2,564	21
Oral cavity and pharynx	1,557	13	1,316	11	1,168	10	4,041	33
Bladder	659	5	115	1	262	2	1,035	9
Kidney and other urinary organs	277	2	63	1	127	1	466	4
Ovary	193	2	321	3	149	1	663	5
Gallbladder and bile ducts	78	1	36	0	13	0	126	1
Larynx	51	0	13	0	45	0	109	1

*Data are millions of Japanese yen (JPY) and US dollars (USD).

in women (¥24,448 million/$202 million).

Table 4 presents the total economic costs of cancer attributable to each of the five modifiable risk factors for both sexes. The economic burden of cancer caused by infection was highest among all modifiable risk factors (¥478,774 million/$3,955 million), followed by active tobacco smoking (¥434,048 million/$3,586 million) and alcohol drinking (¥172,129 million/$1,422 million).

Discussion

This report draws on updated estimates of cancer burden attributable to modifiable factors in Japan in 2015 published by Inoue *et al.* (*8*). Because cancer constitutes 12% of the direct costs of healthcare in Japan as of 2015 (*13*), and 35.4% of the direct medical costs of cancer are associated with lifestyle and environmental factors, controlling the modifiable risk factors may save more than 4% of healthcare costs. Further, this study found that the indirect costs of cancer made up around 46.8% of the total costs. The indirect cost of morbidity in our study is analogous to that in a previous report in Japan in 2011, which estimated this cost to be around ¥295,900 million for men (*33*). On the other hand, our estimate of the indirect morbidity cost in women was higher (¥359,561 million) than their estimate (¥156,900 million) (*33*). This difference is because they used the sex- and age-specific average daily wage, whereas we used the age-specific average daily wage common for both men and women, to take account of the potential full earnings lost according to market value.

Our study found that there were around 1.1 times more male cancer patients than female patients in Japan in 2015, and that the total economic costs of cancer did not considerably differ between men and women. This is because female breast cancer, which is by far the most common female cancer in Japan, accounted for by far the greatest economic burden in terms of not only direct costs but also indirect mortality costs and indirect morbidity costs. Breast cancer begins to occur in working-age women in their 40s (*2*), and the indirect costs of cancer rise when premature deaths occur or patients receive treatment at a younger age. For the same reason, cervical cancer ranked second in indirect morbidity and mortality costs in women although the direct medical costs ranked only 12th among all the cancer sites investigated in this study.

It was not surprising to find that lung, stomach, colon and male prostate cancer incurred a heavy economic burden in terms of both direct medical costs and indirect costs, as these are the most commonly reported types of cancer in Japanese (*2*). Previous reports from the European Union are consistent with our findings - lung cancer showed the highest economic cost followed by breast cancer, colorectal cancer and prostate cancer but not stomach cancer (*10*). In Korea, where *Helicobacter pylori* infection is prevalent (*34*), the economic burden of cancer was heaviest in stomach cancer, followed by liver, lung, and colorectal cancers in 2015 (*11*).

Economic burden attributable to modifiable risk factors

According to our estimation, the economic burden of cancer was highest in cancers that are caused by infection, namely *Helicobacter pylori (H.pylori)* for

Table 4. Breakdown of total economic costs by major modifiable risk factors*, both sexes, Japan, 2015

Cancer Site	Active smoking		Alcohol		Infections		Excess body weight		Physical inactivity	
	JPY	USD	JPY	USD	JPY	USD	JPY	USD	JPY	USD
All cancers	434,048	3,586	172,129	1,422	478,774	3,955	19,041	157	33,726	279
Oral cavity and pharynx	19,951	165	13,049	108	6,933	57	0	0	0	0
Esophagus	28,435	235	29,784	246	0	0	162	1	0	0
Stomach	35,472	293	10,731	89	210,993	1,743	1,110	9	0	0
Colon	16,303	135	33,146	274	0	0	4,619	38	9,890	82
Rectum	12,456	103	21,562	178	0	0	3,082	25	6,991	58
Liver	24,401	202	26,145	216	60,655	501	3,102	26	0	0
Gallbladder and bile ducts	0	0	0	0	0	0	820	7	0	0
Pancreas	19,952	165	0	0	0	0	0	0	0	0
Larynx	6,486	54	2,667	22	0	0	0	0	0	0
Lung, trachea	138,553	1,145	0	0	0	0	0	0	0	0
Breast	0	0	27,186	225	0	0	1,904	16	22,159	183
Cervix uteri	9,241	76	0	0	63,977	529	0	0	0	0
Corpus uteri	0	0	0	0	0	0	270	2	5,896	49
Ovary	0	0	0	0	0	0	0	0	0	0
Prostate	0	0	0	0	0	0	2,992	25	0	0
Bladder	18,809	155	0	0	0	0	0	0	0	0
Kidney and other urinary organs	17,596	145	0	0	0	0	1,029	9	0	0
Malignant lymphoma	0	0	0	0	6,531	54	0	0	0	0
Leukemia	14,873	123	0	0	28,072	232	0	0	0	0

*Data are millions of Japanese yen (JPY) and US dollars (USD). Note that the sum of the economic costs of all risk factors occasionally exceeds the total economic costs presented in Table 2 because of the co-prevalence of multiple risk factors in a person.

stomach cancer (85%) and human papillomavirus (HPV) for cervical cancer in women (100%) (*20*). In other words, ¥210,993 million ($1,743 million) could have been saved if no infection from *H.pylori* had occurred, and ¥63,977 million ($529 million) could have been saved if no one had been infected by HPV in Japan. Further, active tobacco smoking constituted as much as 23.6% in men and 4.0% in women of the total population attributable fraction of cancer incidence in Japan in 2015 (*17*). This implies that a total of ¥434,048 million ($3,586 million) was lost in Japan due to tobacco smoking.

Limitations

Some limitations of this study warrant mention. First, we were not able to consider direct non-medical costs in our analysis. Access to medical facilities to receive treatment varies by geographic region in Japan, where islands are sparsely located, yet the NDB Japan data do not record the place of residence of patients. Therefore, we were unable to estimate distance to medical facilities. Second, although we considered productivity loss due to premature mortality and absenteeism from work, we were not able to estimate the impact of presenteeism (partial loss of productivity on days a patient did work) in our productivity loss estimation due to a paucity of data. Third, we were not able to estimate the informal care provided by family members, because data on the days and hours of informal care for each type of cancer were not available. Nonetheless, this study provides the first evidence on the direct medical costs, indirect morbidity and mortality costs, and costs associated with lifestyle and environmental factors in Japan from a societal perspective.

In conclusion, this study reported that the overall cost of cancer attributable to lifestyle and environmental factors was ¥1,024,006 million ($8,460 million) in Japan in 2015. Productivity loss associated with modifiable factors was highest in stomach cancer in men (¥28,735 million/$237 million) and cervical cancer in women (¥24,448 million/$202 million). Preventing and controlling cancers caused by infections, including *H.pylori* and HPV, and tobacco smoking will not only be life-saving but may also be cost-saving in the long run.

Funding: This study was supported by JSPS KAKENHI Grant Number 16H05244 and the National Cancer Center Research and Development Fund (2021-A-16).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Ministry of Health, Labour and Welfare. Vital Statistics of Japan. *https://www.e-stat.go.jp/stat-search/files?page=1&toukei=00450011&kikan=00450&tstat=000001028897&result_page=1* (accessed January 11, 2023). (in Japanese)
2. National Cancer Center Japan. Cancer Statistics. Cancer Information Service, National Cancer Center, Japan (Vital Statistics of Japan, Ministry of Health, Labour and Welfare) *https://ganjoho.jp/reg_stat/statistics/data/dl/index.html* (accessed January 11, 2023). (in Japanese)
3. Peto J. Cancer epidemiology in the last century and the next decade. Nature. 2001; 411:390-395.
4. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst. 1981; 66:1191-1308.
5. Soerjomataram I, Shield K, Marant-Micallef C, Vignat J, Hill C, Rogel A, Menvielle G, Dossus L, Ormsby JN, Rehm J, Rushton L, Vineis P, Parkin M, Bray F. Cancers related to lifestyle and environmental factors in France in 2015. Eur J Cancer. 2018; 105:103-113.
6. Harvard Report on Cancer Prevention. Volume 1: Causes of human cancer. Cancer Causes Control. 1996; 7 Suppl 1:S3-S59.
7. Wang JB, Jiang Y, Liang H, *et al.* Attributable causes of cancer in China. Ann Oncol. 2012; 23:2983-2989.
8. Inoue M, Hirabayashi M, Abe SK, *et al.* Burden of cancer attributable to modifiable factors in Japan in 2015. Glob Health Med. 2022; 4:26-36.
9. Haga K, Matsumoto K, Kitazawa T, Seto K, Fujita S, Hasegawa T. Cost of illness of the stomach cancer in Japan - a time trend and future projections. Bmc Health Serv Res. 2013; 13:283.
10. Luengo-Fernandez R, Leal J, Gray A, Sullivan R. Economic burden of cancer across the European Union: a population-based cost analysis. Lancet Oncol. 2013; 14:1165-1174.
11. Kim YA, Lee YR, Park J, Oh IH, Kim H, Yoon SJ, Park K. Socioeconomic Burden of Cancer in Korea from 2011 to 2015. Cancer Res Treat. 2020; 52:896-906.
12. Matsumoto K, Haga K, Kitazawa T, Seto K, Fujita S, Hasegawa T. Cost of illness of breast cancer in Japan: trends and future projections. BMC Res Notes. 2015; 8:539.
13. Ministry of Health, Labour and Welfare. Estimates of National Medical Care Expenditure. 2015. *https://www.mhlw.go.jp/english/database/db-hss/enmce.html* (accessed January 11, 2023).
14. Larg A, Moss JR. Cost-of-illness studies: a guide to critical evaluation. Pharmacoeconomics. 2011; 29:653-671.
15. Nishioka Y, Okada S, Noda T, Myojin T, Kubo S, Ohtera S, Kato G, Kuroda T, Ishii H, Imamura T. Absolute risk of acute coronary syndrome after severe hypoglycemia: A population-based 2-year cohort study using the National Database in Japan. J Diabetes Investig. 2020; 11:426-434.
16. Nakajima A, Sakai R, Inoue E, Harigai M. Prevalence of patients with rheumatoid arthritis and age-stratified trends in clinical characteristics and treatment, based on the National Database of Health Insurance Claims and Specific Health Checkups of Japan. Int J Rheum Dis. 2020; 23:1676-1684.
17. Katanoda K, Hirabayashi M, Saito E, Hori M, Abe SK, Matsuda T, Inoue M; the Cancer PAF Japan Collaborators. Burden of cancer attributable to tobacco smoke in Japan in 2015. GHM Open. 2021; 1:43-50.
18. Hirabayashi M, Sawada N, Abe SK, Saito E, Hori M, Katanoda K, Matsuda T, Inoue M; the Cancer PAF Japan Collaborators. Burden of cancer attributable to consumption of alcohol in Japan in 2015. GHM Open. 2021; 1:51-55.

19. Hirabayashi M, Abe SK, Sawada N, Saito E, Hori M, Katanoda K, Matsuda T, Inoue M; the Cancer PAF Japan Collaborators. Burden of cancer attributable to excess bodyweight and physical inactivity in Japan in 2015. GHM Open. 2021; 1:56-62.
20. Lin Y, Wang C, Kikuchi S, Akita T, Tanaka J, Abe SK, Hirabayashi M, Saito E, Hori M, Katanoda K, Matsuda T, Inoue M; the Cancer PAF Japan Collaborators. Burden of cancer attributable to infection in Japan in 2015. GHM Open. 2021; 1:63-69.
21. Takachi R, Ishihara J, Abe SK, Hirabayashi M, Saito E, Hori M, Katanoda K, Matsuda T, Inoue M; the Cancer PAF Japan Collaborators. Burden of cancer attributable to consumption of highly salted food in Japan in 2015. GHM Open. 2021; 1:85-90.
22. Ishihara J, Takachi R, Abe SK, Hirabayashi M, Saito E, Hori M, Katanoda K, Matsuda T, Inoue M; the Cancer PAF Japan Collaborators. Burden of cancer attributable to insufficient vegetable, fruit and dietary fiber consumption in Japan in 2015. GHM Open. 2021; 1:70-75.
23. Abe SK, Takachi R, Ishihara J, Hirabayashi M, Saito E, Hori M, Katanoda K, Matsuda T, Inoue M; the Cancer PAF Japan Collaborators. Burden of cancer attributable to excess red and processed meat consumption in Japan in 2015. GHM Open. 2021; 1:91-96.
24. Hirabayashi M, Nagata C, Abe SK, Sawada N, Saito E, Hori M, Katanoda K, Matsuda T, Inoue M; the Cancer PAF Japan Collaborators. Burden of cancer attributable to exogenous hormone use in Japan in 2015. GHM Open. 2021; 1:97-101.
25. Hirabayashi M, Nagata C, Abe SK, Saito E, Hori M, Katanoda K, Matsuda T, Inoue M; the Cancer PAF Japan Collaborators. Burden of cancer attributable to never breastfeeding in Japan in 2015. GHM Open. 2021; 1:102-105.
26. Hori M, Katanoda K, Ueda K, Nakaya T, Saito E, Abe SK, Hirabayashi M, Matsuda T, Inoue M; the Cancer PAF Japan Collaborators. Burden of cancer attributable to air pollution in Japan in 2015. GHM Open. 2021; 1:76-84.
27. Wu Q, Szatkowski L, Britton J, Parrott S. Economic cost of smoking in people with mental disorders in the UK. Tob Control. 2015; 24:462-468.
28. Ministry of Health, Labour and Welfare. Basic Survey on Wage Structure. *https://www.mhlw.go.jp/english/database/db-l/wage-structure.html* (accessed January 11, 2023).
29. World Health Organization. Making choices in health: WHO guide to cost-effectiveness analysis. *https://apps.who.int/iris/handle/10665/42699?locale-attribute=en&* (accessed January 11, 2023).
30. Hanly P, Timmons A, Walsh PM, Sharp L. Breast and prostate cancer productivity costs: a comparison of the human capital approach and the friction cost approach. Value Health. 2012; 15:429-436.
31. Ministry of Health, Labour and Welfare. Patient Survey 2014. *https://www.mhlw.go.jp/toukei/saikin/hw/kanja/14/index.html* (accessed January 11, 2023). (in Japanese)
32. Statistics Bureau of Japan. Labour Force Survey 2015. *https://www.e-stat.go.jp/en/stat-search/files?page=1&layout=datalist&toukei=00200531&tstat=000000110001&cycle=7&year=20150&month=0&tclass1=000001040276&tclass2=000001040283&tclass3=000001040284&result_back=1&tclass4val=0* (accessed January 11, 2023).
33. Fukuda K. Estimation of productivity loss due to cancer incidence. 2012-13 Ministry of Health, Labour and Welfare Research Grant Report. *https://hospital.luke.ac.jp/about/approach/doc/ra21/2/research_activities_2_6.doc* (accessed January 11, 2023). (in Japanese)
34. Leja M, Grinberga-Derica I, Bilgilier C, Steininger C. Review: Epidemiology of Helicobacter pylori infection. Helicobacter. 2019; 24 Suppl 1:e12635.

Received January 11, 2023; Revised March 24, 2023; Accepted April 11, 2023.

Released online in J-STAGE as advance publication May 4, 2023.

**Address correspondence to*:
Eiko Saito, Institute for Global Health Policy Research, Bureau of International Health Cooperation, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: esaito@it.ncgm.go.jp

Global Health & Medicine. 2023; 5(4):246-248.
COMMENTARY
DOI: 10.35772/ghm.2023.01020

Sorafenib and surgery for hepatocellular carcinoma – a controversial relation: Lesson learned?

Guido Torzilli[1,2,*]

[1] Department of Biomedical Sciences, Humanitas University, Milan, Italy:
[2] Division of Hepatobiliary & General Surgery, Department of Surgery - IRCCS, Humanitas Research Hospital, Milan, Italy.

Abstract: Sorafenib is a breakthrough in the medical treatment aiming to control hepatocellular carcinoma (HCC) progression, but there is some controversy in patients' selection. The introduction of Sorafenib has led to several positive effects. New more than promising antiangiogenic molecules have followed. Immunotherapy combined with antiangiogenic therapy has also strongly entered into the treatment of HCC. All of that has induced a significant guideline revision profiling Sorafenib as a second line systemic therapy in the event of advanced HCC. However, for those patients with advanced but resectable HCC, the selection of surgery or systemic therapy should be reviewed and reconsidered.

***Keywords*:** HCC, Sorafenib, hepatectomy, cirrhosis

Sorafenib represents the first medical treatment aiming to control hepatocellular carcinoma (HCC) progression with some success. Without any doubt, it is a breakthrough in the management of this tumor. As a matter of fact, it represents a boost for the scientific community. A pillar indicating the mainstream has followed, and from which nowadays many other more than promising drugs have grown up. Apparently, just a virtuous story, in reality a story hiding a modality, which the scientific community should review and reconsider.

The story started literally as follows. The first release showing the potential role of Sorafenib was the paper of Llovet *et al*. published in 2008 (*1*). Patients' selection was disclosed as follows: "The study population consisted of patients with advanced-stage hepatocellular carcinoma, as confirmed by pathological analysis. None of the patients had received previous systemic therapy. Patients were classified as having advanced disease if they were not eligible for or had disease progression after surgical or locoregional therapies". The target population was then clearly stated and could be disclosed also as follows: any HCC not suitable for surgery or any other locoregional therapy or progressing after these treatments would have been eligible for the study. Then, everyone may agree that the background population was not including all those patients operated on for HCC independently from the degree of organ invasion. That paper did not capture those patients with HCC even multinodular or with vascular invasion who were treated successfully surgically, because they were not even seen. In the same year that population, unseen by the aforementioned study, appeared in two reports showing the benefit of the surgical treatment for those patients (*2,3*): those patients were those carriers of multiple HCC or HCC with macrovascular invasion. These patients before the cited reports (*1-3*) were classified in the Barcelona Clinic Liver Cancer (BCLC) staging classification (*4*) as just amenable for palliation. However, given all of that the term palliation was changed in medical treatment both in the new BCLC versions (*5*), and in the treatment recommendation of the European Association for the Study of the Liver (EASL) guidelines (*6*). The die was cast and surgery for advanced and multinodular HCC had no room, despite the population explored by Llovet *et al* did not catch that patients' profile, and other reports were emphasizing the role of resection for them (*2,3*). In 2013, a large multi-institutional series collecting more than the 2000 consecutive patients operated on for HCC in 10 tertiary referral centers worldwide distributed, showed how advanced and multinodular presentations represented half of those operated on, and outcome was anything but negligible (*7*). That report strongly suggested to the community that there was a dark matter, which was not represented in the guidelines because of the inadvertent mismatch of different populations once the guidelines were released (*6*). Several confirmatory reports followed (*8-11*). All of them strongly claimed to reconsider the recommendations, suggesting the existence of another population of patient carriers of multinodular and advanced HCC but profitably amenable to surgical treatment. However, the 2018 EASL guidelines literally reported as follows: "Liver resection

can only be considered for PV1/2 extension of HCC, and only then as an option to be tested within research settings and not to be considered a standard of practice" (*12*). Then, a surgical approach despite its consolidated, and reproducible short and long-term results obtained dealing with a patients' population overtly missed by the study of Llovet *et al*. (*1*), was officially addressed as an experimental procedure. Inversely, Sorafenib raised the standard of care for treatment of multinodular and advanced HCC because the high level of evidence of the report sustaining that. A report, for sure methodologically perfect, but overtly referred just to a portion of the population of patients with advanced or multinodular HCC: those who were unresectable. Then, a study perfect to prove the role of Sorafenib, but fairly useless for drawing any reliable conclusion about the role of surgery in patients with advanced and multinodular HCC was conducted.

Undoubtedly, the introduction of Sorafenib has led to several positive effects. New more than promising antiangiogenic molecules have followed (*13*). Immunotherapy combined with antiangiogenic therapy has strongly entered into the treatment of HCC, too (*14*). All of that has induced a significant guidelines revision (*15*) profiling Sorafenib as a second line systemic therapy in the event of advanced HCC. Concerning surgery nothing changed. That, despite, progress in the systemic treatment rather than displacing surgery as previously are even leading some authors to consider surgery for that patients' population carriers of unresectable advanced and multinodular HCC, which was the population considered in the study of Llovet *et al*. (*1,16,17*). Then, at the end, surgery has gained relevance just by the improvements of systemic treatments, which initially and inappropriately displaced it (*18*). However, in the last decade and somehow until now, a potentially curative treatment as surgery is, even for patients with advanced HCC, has not been considered by a consistent part of the medical community. The medical community should be warned of that. Nevertheless, the latest report seems reluctant to reconsider the recommendations accordingly (*15*). The different population considered by Llovet *et al*. (*1*), the patient carriers of unresectable advanced HCC, remains the only group of patients considered, while those patients with advanced but resectable HCC remains unseen and not represented in the recommendations. A misinterpretation, which should be admitted, recognized, and not repeated: hopefully, these few words may help.

Funding: None.

Conflict of Interest: The author has no conflicts of interest to disclose.

References

1. Llovet JM, Ricci S, Mazzaferro V, *et al*. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008; 359:378-390.
2. Torzilli G, Donadon M, Marconi M, Palmisano A, Del Fabbro D, Spinelli A, Botea F, Montorsi M. Hepatectomy for stage B and stage C hepatocellular carcinoma in the Barcelona Clinic Liver Cancer classification: Results of a prospective analysis. Arch Surg. 2008; 143:1082-1090
3. Ishizawa T, Hasegawa K, Aoki T, Takahashi M, Inoue Y, Sano K, Imamura H, Sugawara Y, Kokudo N, Makuuchi M. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. Gastroenterology. 2008; 134:1908-1916
4. Llovet JM, Fuster J, Bruix J; Barcelona-Clínic Liver Cancer Group. The Barcelona approach: Diagnosis, staging, and treatment of hepatocellular carcinoma. Liver Transpl. 2004; 10:S115-S120.
5. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet. 2012; 379:1245-1255
6. European Association for the Study of the Liver; European Organization for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: Management of hepatocellular carcinoma. J Hepatol. 2012; 56:908-943
7. Torzilli G, Belghiti J, Kokudo N, Takayama T, Capussotti L, Nuzzo G, Vauthey JN, Choti MA, De Santibanes E, Donadon M, Morenghi E, Makuuchi M. A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: Is it adherent to the EASL/AASLD recommendations? An observational study of the HCC East-West study group. Ann Surg. 2013; 257:929-937
8. Kokudo T, Hasegawa K, Yamamoto S, Shindoh J, Takemura N, Aoki T, Sakamoto Y, Makuuchi M, Sugawara Y, Kokudo N. Surgical treatment of hepatocellular carcinoma associated with hepatic vein tumor thrombosis. J Hepatol. 2014; 61:583-588.
9. Roayaie S, Jibara G, Tabrizian P, Park JW, Yang J, Yan L, Schwartz M, Han G, Izzo F, Chen M, Blanc JF, Johnson P, Kudo M, Roberts LR, Sherman M. The role of hepatic resection in the treatment of hepatocellular cancer. Hepatology. 2015; 62:440-451.
10. Park JW, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, Kudo M, Johnson P, Wagner S, Orsini LS, Sherman M. Global patterns of hepatocellular carcinoma management from diagnosis to death: The BRIDGE Study. Liver Int. 2015; 35:2155-2166.
11. Famularo S, Donadon M, Cipriani F, *et al*. Hepatectomy versus Sorafenib in advanced nonmetastatic hepatocellular Carcinoma: A real-life multicentric weighted comparison. Ann Surg. 2022; 275:743-752.
12. European Association for the Study of the Liver; European Association for the Study of the Liver. EASL clinical practice guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018; 69:182-236.
13. Kudo M, Finn RS, Qin S, *et al*. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: A randomised phase 3 non-inferiority trial. Lancet. 2018; 391:1163-1173.
14. Finn RS, Qin S, Ikeda M, *et al*. Atezolizumab plus Bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020; 382:1894-1905.
15. Reig M Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado A, Kelley RK, Galle P, Mazzaferro V, Salem R, Sangro B, Singal A, Vogel A, Fuster J, Ayuso C, Bruix J. BCLC strategy for prognosis prediction and

treatment recommendation: The 2022 update. J Hepatol. 2022; 76:681-693.
16. Yoshimoto T, Imura S, Morine Y, Ikemoto T, Arakawa Y, Iwahashi S, Saito YU, Takasu C, Ishikawa D, Teraoku H, Bando Y, Shimada M. The outcome of sorafenib therapy on unresectable hepatocellular carcinoma: Experience of conversion and salvage hepatectomy. Anticancer Res. 2018; 38:501-507.
17. Tomonari T, Sato Y, Tanaka H, Tanaka T, Taniguchi T, Sogabe M, Okamoto K, Miyamoto H, Muguruma N, Saito Y, Imura S, Bando Y, Shimada M, Takayama T. Conversion therapy for unresectable hepatocellular carcinoma after lenvatinib: Three case reports. Medicine (Baltimore). 2020; 99:e22782.
18. Vitale A, Trevisani F, Farinati F, Cillo U. Treatment of Hepatocellular Carcinoma in the precision medicine era: From treatment stage migration to therapeutic hierarchy. Hepatology. 2020; 72:2206-2218.

Received March 16, 2023; Accepted May 14, 2023.

Released online in J-STAGE as advance publication May 23, 2023.

Address correspondence to:
Guido Torzilli, Division of Hepatobiliary & General Surgery, Department of Surgery - IRCCS, Humanitas Research Hospital, via Manzoni 56, 20089 Rozzano, Milan, Italy.
E-mail: guido.torzilli@hunimed.eu

Global Health & Medicine. 2023; 5(4):249-254.

DOI: 10.35772/ghm.2023.01031

International cooperation for nursing human resource development in Lao PDR: Investing in nursing leadership

Kyoko Koto-Shimada[1,2,*], Kazuki Miyazaki[2], Pengdy Inthapanith[3], Souksavanh Phanpaseuth[3,4], Anousone Sisoulath[3,4], Shiori Nagatani[1] , Shikino Kikuchi[1,2], Toyomitsu Tamura[2], Noriko Fujita[2,5]

[1] Project for Sustainable Development and Quality Assurance of Healthcare Professionals, JICA Lao PDR;
[2] Bureau of International Health Cooperation, National Center for Global Health and Medicine, Tokyo, Japan;
[3] Nursing and Midwifery Board, Healthcare Professional Council, Ministry of Health, Lao PDR;
[4] Faculty of Nursing Sciences, The University of Health Sciences, Lao PDR;
[5] School of Tropical Medicine and Global Health, Nagasaki University, Japan.

Abstract: Strengthening nursing leadership in health systems has been identified as a priority for achieving Universal Health Coverage (UHC). We aimed to analyse the characteristics of Japanese technical assistance projects for nursing human resource development in Lao People's Democratic Republic (Lao PDR) and suggest directions for future assistance. An upgrading program, as part of human resource development, was initiated in the 1990s; it has contributed to the development of nursing leaders. Moreover, technical assistance from development partners has had synergistic effects by consistently promoting the involvement of nursing leaders in administration, education, and clinical practice to establish a functional regulatory system. In resource-limited settings, the application of both edge-pulling (leadership development) and bottom-up (quality improvement of the mass population) strategies are required. From a long-term perspective, development partners should continue to invest in increasing the number and quality of nursing leaders by upgrading the courses and leadership training programs, starting from the younger generation.

***Keywords*:** leadership, nursing, capacity building, strategic planning

Introduction

Strengthening nursing leadership in health and academic systems is the priority for achieving Universal Health Coverage (UHC) and other health goals, as stated in the Global Strategic Directions for Nursing and Midwifery 2021–2025 (*1*). The first State of the World's Nursing Report revealed the need for investments in leadership development of both current and future leaders to ensure that nurses have an influential role in the health policy formulation and decision-making, together with a massive acceleration of nursing education and the creation of nursing jobs to address the projected shortage and inequitable distribution of nurses worldwide (*2*).

The Japanese Official Development Assistance program has been providing technical and financial support for the capacity development of nurses and midwives since the 1990s. Technical advisors on nursing were sent to Lao People's Democratic Republic (Lao PDR), Vietnam, Cambodia, and Myanmar, among other Southeast Asian countries. The cooperation initially focused on improving nursing management and in-service training in the hospital settings, and then expanded to strengthening the health system including the primary health care settings. Since the 2000s, the development of a regulatory framework for a registration and licensing system has been a common goal, as the Association of Southeast Asian Nations (ASEAN) member states have signed Mutual Recognition Arrangements. Moreover, enhancing the capacity of educators/trainers and leadership development has been the current focus to ensure the safety and quality of healthcare services (*3*).

We aimed to analyse the characteristics of Japanese technical assistance projects for nursing in Lao PDR and suggest directions for future assistance in nursing human resource development.

Table 1 shows the chronology of regulations and policies related to human resources for health, education programs for nurses, regulations for nursing education and services, and Japanese technical assistance in Lao PDR, explaining how these regulations and policies related have emerged.

Ensuring the quality of healthcare professionals

The Government of Lao PDR has committed to establishing an effective system to ensure UHC by

Table 1. Evolution and chronology of human resources for health- and nursing-related issues, and technical assistance projects for nursing*

Years	Regulations/policies related to Human Resources for Health	Education Program for Nurses	Regulations related to Nursing Education and Services	Technical assistance projects for nursing by Japanese Official Development Assistance
Before 2004		1950s- 2002 Auxiliary nurses as low- level 1960s- 2010 Diploma of nursing and technical nursing as middle - level 1990s -2014 Upgrading program to Bachelor of Science in Nursing in Thailand 2003- on-going Bridging program low- to middle- level		
2005	Law on Health Care (No. 09/NA)			Project for Human Resources Development of Nursing and Midwifery; - Strengthened nursing and midwifery administration including establish fundamental regulations - Strengthened the nursing education system including develop school implementation guideline
2006	ASEAN Mutual Recognition Arrangement on Nursing Services			
2007			Nursing and Midwifery Regulations (No. 0656/MoH) Scope of Nursing Practice (No.40/MoH)	
2008			Nursing/Midwifery School Management and Implementation Guidelines (No.0039/MoH)	
2009		Higher Diploma of Nursing as high- level		
2010		Upgrading program to high- level		
2011	Health Personnel Development Strategy by 2020 (No. 831/MoH)	Bachelor of Science in Nursing		
2012				Project for Sustainable Development of Human Resource for Health to Improve Maternal, Neonatal and Child Health Services; - Institutionalization of the nursing education system - Capacity building of nursing education institutions - Strengthening the coordination mechanism for improving the nursing education system
2013		Higher Diploma of Nursing (Revised) to be competency-based	National Competencies for Licensed Nurses in Lao PDR (No.1132/MoH)	
2014	Law on Health Care (Amended) (No. 58/NA) Health Sector Reform Framework Laos 2013-2025 (No. 029/GOV)			
2015	Strategy on Healthcare Professional Licensing and Registration System in Lao PDR 2016-2025 (No. 2098/MoH)		Scope of the Nursing Practice (Revised) (No.0726/MoH)	
2016	The 8th Health Sector Development Plan (2016–2020)		Instruction for Management and Implementation of Non-University Higher Education Institution for Health (No. 0176/MoH)	
2017	Ministerial Decision on Licensing and Registration of Healthcare Professionals in Lao PDR (No. 1307/MoH) Ministerial Decision on Health Care Professional Council (No.0131/MoH)	Upgrading program to Bachelor of Science in Nursing (in-country)		
2018			Ministerial Decision on Approval and Implementation of Quality Assurance of Higher Diploma Education (No. 1118/MoH)	Project for Sustainable Development and Quality Assurance of Health care Professionals; - Establishment legislation for registration and licensing system

*Data Source: Official documents released by the Ministry of Health in Lao PDR and JICA project reports, unavailable online.

Table 1. Evolution and chronology of human resources for health- and nursing-related issues, and technical assistance projects for nursing* (continued)

Years	Regulations/policies related to Human Resources for Health	Education Program for Nurses	Regulations related to Nursing Education and Services	Technical assistance projects for nursing by Japanese Official Development Assistance
2019	Instruction on the implementation of the registration and licensing healthcare professionals in transition period by 2020 without taking the national examination (No.0182/HPC)		Decision on Endorsement of Professional Code of Ethics for Nurses and Midwives (No.0147/HPC)	- Implementation of the National Examination Nurses and Midwives - Implementation of Professional Internship Program for Nurses
2020	The 9th Five Year Health Sector Development Plan (2021-2025) Instruction on Implementation of Registration and Licensing of Healthcare Professionals (No. 0108/HPC)			
2021	Decision on the admission of students in the field of public health both domestically and abroad (No. 2541/MoH)		Decision on Approval of the National Examination for Nurses and Midwives in 2020 (No. 007/HPC) Decision on National Competency for Licensed Nurses in Lao PDR (Revised) (No. 0104/HPC)	
2022	Health Sector Reform Strategy 2021-2030 (No.2645/MoH)		Decision on Approval of the Implementation of Professional Internship Program for Nurses 2021 (No.016/HPC)	

*Data Source: Official documents released by the Ministry of Health in Lao PDR and JICA project reports, unavailable online.

2025 since the adoption of the Health Sector Reform Framework in 2014, and its revision in 2022, which were the official documents unavailable online. In this framework, human resources for health are one of the five pillars in the Strategy to achieve UHC: health service delivery, governance, management, coordination, health financing, health information, planning, monitoring, and evaluation. Aligned with the Health Sector Reform Framework, the Lao PDR Ministry of Health (MoH) has been developing and implementing an action plan called the Health Sector Development Plan every 5 years (2016; 2020), which were the official documents unavailable online. In this plan, health personnel management, health personnel development, and health science research are part of the national programs (2020).

In 2015, the MoH implemented the Strategy on Healthcare Professional Licensing and Registration System in Lao PDR 2016–2025 to ensure the safety and quality of healthcare providers. Until then, graduation was the only requirement to be deployed by the MoH as healthcare personnel, due to the absence of a licensing system (*4*). Subsequently, the MoH reappointed the Healthcare Professional Council, which played a key role in endorsing the regulations necessary to develop the new system in 2017. These include the registration and licencing of current healthcare professionals who meet the qualifications, the conduct of licencing examinations for new graduates, and the implementation of standards for foreign healthcare practitioners following the requirements of the ASEAN Mutual Recognition Arrangements which was signed in 2006. Furthermore, the MoH is currently revising the Law on Health Care (2005; 2014) in accordance with the licencing system and developing a new Health Personnel Development Strategy (2011).

Nursing human resource development

Lao PDR is a lower-middle-income country located in the Indochina Peninsula, with a population of 7.4 million in 2021. Rural residents accounted for 63% of the population in 2021 (*5*). A total of 7,930 (40% of the total health workers) nursing workers were in the public sector in 2020, which eventually increased to 7,115 (36%) in 2014, according to the Annual Report on Health Personnel Distribution 2019–2020 and 2014 which were official documents released by MoH, not available online. During this period, the ratio per 1,000 population remained 1:1. Approximately 64% of the nursing workforce were assigned in the district and health centre levels, providing primary healthcare services. Currently, two professional educational programs for nurses are available: a 4-year bachelor's course and a 3-year higher diploma course. Since 2011, the bachelor's course has been offered only in the Faculty of Nursing Sciences, University of Health

Sciences, in the capital of Vientiane. Higher diploma courses that were introduced in 2009 are currently offered in eight provincial-level educational institutions. Both courses require 12 years of general education for admission (*6*).

The Ministry of Home Affairs divided the public sector health workforce into three levels according to the status of civil servants: high, middle, and low. Nurses who completed the above programs were categorised as high-level nurses, accounting for 22% of the nursing workforce. The other 55% and 23% of the nurses were in the middle- and low-level nursing workforce, as they had completed the previous educational programs within less than 3 years, referred to the Annual Report on Health Personnel Distribution 2019–2020 which was official documents released by MoH, not available online. Therefore, educational institutions have been continuously offering courses to nurses who want to achieve a higher diploma and bachelor's degree since 2010 and 2017, respectively (*6*). From 1990, four batches of Laotian nurses were able to complete a bachelor's degree in Thailand (personal communication with Nursing and Midwifery board members, 2023). A joint program with Konkaen University, Thailand, started in-county continuous courses in 2002 at the Faculty of Nursing Sciences, University of Health Sciences, to support nurses achieve a bachelor's degree (*7*). Most graduates who completed this program took master's and PhD programs overseas under the official recognition of the MoH.

As of 2020 in Health Personnel Information Management System, 28 nurses completed a master's degree or higher in nursing. As they are considered highly educated, they became the leaders of the workforce in terms of the administrative, educational, and clinical aspects. However, the younger generation was underrepresented; none of the 28 nurses included those aged < 30 years, 25% were between 31 to 45 years old, and half were 50 years and older. Due to the limited health budget, young nurses must spend several years working as volunteers or contract staff status to be recruited as civil servants. Civil servants' status is a requirement criterion for upgrading opportunities. Therefore, the chances for upgrading for younger generations were minimal (*8*).

Technical assistance projects for nurses to strengthen the human resource development by the Japanese Official Development Assistance

In Lao PDR, technical assistance projects for nurses, implemented by the Japan International Cooperation Agency under the Japanese Official Development Assistance (hereafter, the project), were initiated in 2005 to strengthen the human resource development system in terms of the administrative, educational, and clinical aspects. The first project supported the development of nursing and midwifery regulations as a foundation for providing professional services by stipulating the scope of nursing practice (2007), establishing management and implementation guidelines of quality assurance for nursing educational institutions (2008), and developing a guidebook on fundamental nursing practice to improve the quality of nursing education.

The second project involved the development of a national competency framework for licenced nurses (2013), the revision of the associate diploma curriculum into a competency-based curriculum (2013), and the provision of various training programs for nurse educators and clinical instructors to bridge the gap between actual nursing services and stipulated regulations (2015; 2016). Meanwhile, the project supported the development of the abovementioned national strategy for the registration and licencing of healthcare professionals in 2015 (*3*).

Following the above strategy, the third project aims to establish a licencing system in Lao PDR. Fulfilling the criteria of the ASEAN Mutual Recognition Arrangements, the Nursing and Midwifery board (hereafter, the board) of the Healthcare Professional Council has developed various official documents (*e.g.*, decisions and instructions) to establish registration and licensing system, including National Licensure Examination and Professional Internship Program from 2017. Three rounds of National Licensure Examination as a competency assessment since 2020 has been conducted. The examination committee, consisting of board members, faculty members, and clinical leaders, developed an examination blueprint in line with the curriculum and course syllabus; created a question bank; and examined the quality of questions using indicators such as the rate of correct answers and quality index. According to the cycle management system, the quality of examination questions improved gradually (*9*). In addition to the written licensure examination, the MoH implemented a mandatory clinical internship training program to ensure clinical nursing competency since 2022. To this end, the board revised the competency framework following the ASEAN core competencies (2021) and developed an 8-month training curriculum. Central and selected provincial hospitals have offered this training program to those who passed the above examinations. The project supported providing trainings for clinical instructors in conducting clinical teaching for new graduates and strengthening the training management system by enabling central hospitals to provide supportive supervision to provincial hospitals. In December 2022, the first cohort of 37 new graduates who completed the program received their professional licences, marking the achievement of a milestone in the new registration and licencing system of Lao PDR. Moreover, other healthcare boards under the Healthcare Professional Council followed suit with the lessons

learned to establish this new system, modelling the efforts of the board and the project.

Nursing leaders' involvement in the improvement of healthcare services

Nursing leaders in administration, education, and clinical practice have contributed to the strengthening of healthcare services in Lao PDR. Currently, they play vital and responsible roles in decision-making under the MoH, such as deputy directors of hospitals and deans and vice deans of educational institutions. They are also actively cooperating with various development partners, including multilateral and bilateral organisations and non-governmental organisations, to respond to the healthcare needs of the diverse population in Lao PDR. They also follow the requirements of the ASEAN Joint Coordination Committee and directions from the global nursing community. With the support of the Thailand International Cooperation Agency, nursing leaders are currently developing a clinical nursing leadership competency framework. In the future, they aim to establish the National Nursing Association as one of the three pillars, along with the Government Chief Nursing Officer and the board. One of the core nursing leaders stated, *"We are looking at the same direction to improve the quality of nursing care in Lao PDR"*. This is one of the strengths of the human resource development system in the Lao PDR, which leverages and enhances the nursing leaders' solidarity.

Further improvement and necessary investment for nursing human resource development

The long-term perspective and commitment of the MoH has played a substantial role in the development and implementation of healthcare policies (*10*). Needless to say, the MoH's strategy of offering bridging courses to prepare for higher degrees in nursing since the 1990s has contributed to the development of nursing leaders. Technical assistance from development partners has had synergistic effects by consistently promoting the involvement of nursing leaders in the administration, education, and clinical practice in establishing a functional regulatory system for nursing professionals and providing services in resource-limited settings for 20 years. Nursing leaders are essential in driving implementation and linking all necessary regulatory functions (*11,12*). The development of human resources in low- and middle-income countries requires the application of edge-pulling (leadership development) and bottom-up (quality improvement of the mass population) strategies based on long- and middle-term perspectives (*13*). Furthermore, nursing leaders are expected to contribute to evidence-based policy-making in workforce governance and management (*1*).

Therefore, in line with the government policies as the Ministry of Health mitigated criteria for upgrading courses (2021), development partners should continue to invest in increasing the number and quality of nursing leaders through upgrading courses (*14*) and leadership training programs (*15*) starting from the younger generation (*1*), in collaboration with academic institutions and professional organisations. While the Lao Women's Union has played a central role in developing and promoting the status of women for over 40 years, and the Lao PDR government has made progress in adapting Law on Gender Equity (No.77/NA, 2019) to enhance gender equality in political participation, economic opportunities, education, labour and social protection (*16*), many female leaders are reluctant to take up chances because of their life courses. Thus, it is important for further gender considerations should be taken into account, in line with the Lao PDR government's efforts as a principle for the implementation of Official Development Assistance (*17*). Such investments would contribute to the achievement of UHC and education, gender equality, decent work, and inclusive economic growth among the targets for Sustainable Development Goals (*2*).

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. World Health Organization. Global Strategic Directions for Nursing and Midwifery 2021–2025. *https://www.who.int/publications/i/item/9789240033863* (accessed April 6, 2023).
2. World Health Organization. State of the world's nursing 2020: investing in education, jobs and leadership. *https://www.who.int/publications/i/item/9789240003279* (accessed April 6, 2023)
3. Hashimoto C. Future recommendation from 25-year nursing projects implemented by NCGM. In: Nursing human resources development in Cambodia, Laos PDR, Vietnam, and Myanmar and Mutual Recognition Arrangement (MRA) in ASEAN. Bureau of International Health Cooperation, National Center for Global Health and Medicine, Tokyo, Japan, 2018;38- 48. *https://kyokuhp.ncgm.go.jp/library/tech_doc/2018/Technical_Report_11_light.pdf* (accessed December 1, 2022). (in Japanese)
4. Ministry of Health. Strategy on Healthcare Professional Licensing and Registration System in Lao PDR 2016–2025 (Official translation in English). Vientiane: Lao PDR; 2016. *https://hpc.gov.la/la/legislations* (accessed August 1, 2022)
5. The World Bank. Data for Lao PDR. *https://data.worldbank.org/?locations=LA-XN* (accessed March 19, 2023)
6. Phanpaseuth, S. Nursing Education in Lao PDR. In: Enhancing Nursing Service and Nursing Education in ASEAN (Aungsuroch Y, eds). Faculty of Nursing,

Chulalongkorn University, Bangkok, Thailand, 2016; 118-130. *https://sigma.nursingrepository.org/handle/10755/622928* (accessed March 19, 2023)
7. Matsuo J, Mouioudomde P, Akazawa, C. The change of nursing education in Lao People's Democratic Republic. Journal of Nursing Research. 2017; 7:114-123. (in Japanese)
8. Qian Y, Yan F, Wang W, Clancy S, Akkhavong K, Vonglokham M, Outhensackda S, Østbye T. Challenges for strengthening the health workforce in the Lao People's democratic Republic: Perspectives from key stakeholders. Hum Resour Health. 2016; 14:72.
9. Tamura T, Miyazaki K. Establishment of the Quality Assurance Mechanism for Nurses in Low- and Middle-Income Countries -Creation and Implementation of the National Licensure Examination in Lao PDR-. Bureau of International Health Cooperation, National Center for Global Health and Medicine, Tokyo, Japan, 2022. *https://kyokuhp.ncgm.go.jp/library/tech_doc/PDF_JPG/technical_ReportVol14.pdf* (accessed March 1, 2022) (in Japanese)
10. Sonoda M, Syhavong B, Vongsamphanh C, Phoutsavath P, Inthapanith P, Rotem A, Fujita N. The evolution of the national licensing system of health care professionals: A qualitative descriptive case study in Lao People's Democratic Republic. Hum Resour Health. 2017; 15:51.
11. Michaels-Strasser S, Smith J, Khanyola J, Sutton R, Price T, El Sadr WM. Strengthening the quality and quantity of the nursing and midwifery workforce: Report on eight years of the NEPI project. Ann Glob Health. 2018; 84:31-35.
12. Matsuoka S, Fujita N, Koto-Shimada K, Zwi AB. Regulation of nursing professionals in Cambodia: Strategies to overcome underpinning challenges. Int Nurs Rev. 2021; 68:399-411.
13. Koto-Shimada K, Yanagisawa S, Boonyanurak P, Fujita N. Building the capacity of nursing professionals in Cambodia: Insights from a bridging programme for faculty development. Int J Nurs Pract. 2016; Suppl 1:22-30.
14. Fujita N, Matsuoka S, Koto-Shimada K, Ikarashi M, Hazarika I, Zwi AB. Regulation of nursing professionals in Cambodia and Vietnam: A review of the evolution and key influences. Hum Resour Health. 2019; 17:48.
15. Salvage J, White J. Nursing leadership and health policy: Everybody's business. Int Nurs Rev. 2019; 66:147-150.
16. UNDP Lao PDR. Gender Equality Strategy 2022-2026. *https://www.undp.org/sites/g/files/zskgke326/files/2022-11/undp_lao_pdr_gender_strategy_and_action_plan_2022-2026-signed.pdf* (accessed July 16, 2023)
17. Ministry of Foreign Affairs of Japan, Country Assistance Policy. 2019. *https://www.mofa.go.jp/mofaj/gaiko/oda/files/000072258.pdf* (accessed July 16, 2023) (in Japanese)

Received March 30, 2023; Revised July 20, 2023; Accepted August 3, 2023.

Released online in J-STAGE as advance publication August 9, 2023.

**Address correspondence to*:
Kyoko Koto-Shimada, Project for Sustainable Development and Quality Assurance of Healthcare Professionals (DQHP), C/O JICA Laos Office, P.O Box 3933, Vientiane, Lao PDR.
E-mail: kyshimada@it.ncgm.go.jp

Global Health & Medicine. 2023; 5(4):255-256. LETTER

DOI: 10.35772/ghm.2023.01010

Underlying background of the current trend of increasing HPV vaccination coverage in Japan

Mira Namba[1,§], Yudai Kaneda[2,§,*], Chiharu Kawasaki[3], Rajeev Shrestha[4], Tetsuya Tanimoto[5]

[1] School of Medicine, Keio University, Tokyo, Japan;
[2] School of Medicine, Hokkaido University, Hokkaido, Japan;
[3] School of Medicine, Teikyo University, Tokyo, Japan;
[4] Palliative care and Chronic disease, Green Pasture Hospital, Pokhara, Nepal;
[5] Department of Internal Medicine, Jyoban Hospital of Tokiwa Foundation, Fukushima, Japan.

Abstract: Cervical cancer is prevalent among women, with a reported 604,127 cases in 2020 worldwide. The incidence of cervical cancer has been mitigated in most high-income countries by promoting the human papilloma virus (HPV) vaccine. However, in Japan, cervical cancer is still a leading cause of mortality and the most prevalent cancer among women aged between 15 and 39. This can be attributed to the 7-year suspension of HPV vaccination recommendations by the Japanese government. A decline in vaccination coverage followed this suspension, caused by a small number of reported adverse events, resulting in a steep decline in vaccination coverage from over 70% to less than 1%. However, there have been indications of a change in trend in Japan. In 2020, a group of volunteer doctors initiated awareness-raising activities through social networking services and other platforms, and the target population that received at least one dose of the vaccine in 2020 increased to 15.9%. Additionally, in July 2020, the Japanese government approved the updated 9-valent HPV vaccine and resumed recommendations in November 2021. As a result, 30.1% of those eligible for routine HPV vaccination received at least one dose of the vaccine from April to September, 2022. However, the HPV vaccine coverage in Japan is still far from the 90% recommended by the World Health Organization, and continued communication and education on the vaccine's benefits are necessary to achieve optimal coverage.

***Keywords*:** HPV vaccine, vaccination coverage, cervical cancer, Japan

Cervical cancer is the fourth most common cancer in women, with an estimated 604,127 reported cases in 2020 worldwide (*1*). Still, the incidence has been mitigated in most high-income countries through the promotion of the human papilloma virus (HPV) vaccine (*2*). Unfortunately, this is not the case in Japan, where cervical cancer is still the second leading cause of mortality and the most prevalent form of cancer among women aged between 15 and 39 (*3*).

The dire situation can be partly attributed to the 7-year-long suspension of proactive recommendations for HPV vaccination by the Japanese government. Despite the implementation of a government-subsidized HPV vaccination program in 2010 and its establishment as a routine, a publicly-funded vaccine for girls aged 12 to 16 years since April 2013, the immediate suspension of public recommendations since June 2013 due to a small number of reported adverse events resulted in a steep decline in vaccination coverage, which plummeted from over 70% to less than 1% in a birth fiscal year cohort and persisted for nearly seven years (*4*). However, as Figure 1, which shows the trend of HPV vaccination coverage among the target population in Japan using publicly available data from the Ministry of Health, Labor and Welfare website (*5*), suggests, there are indications that this trend is reversing in Japan.

In 2020, a volunteer group of doctors initiated awareness-raising activities on the issue through social networking services and other platforms such as Twitter (*6*), leveraging accumulated domestic scientific evidence that had been amassed over the preceding seven years, which revealed there was no association between HPV vaccine and reported post-vaccination symptoms (*7*). In the case of vaccination against coronavirus disease 2019 (COVID-19), such activities were reported to have reduced Japanese university students' vaccine hesitancy (*8*), and similar results were likely achieved with regard to HPV vaccination. Indeed, the target population that received at least one dose of the vaccine in the fiscal year 2020 increased to 15.9% from 3.3% in the previous year.

Subsequently, the Japanese government changed its policy; it approved the updated 9-valent HPV vaccine in

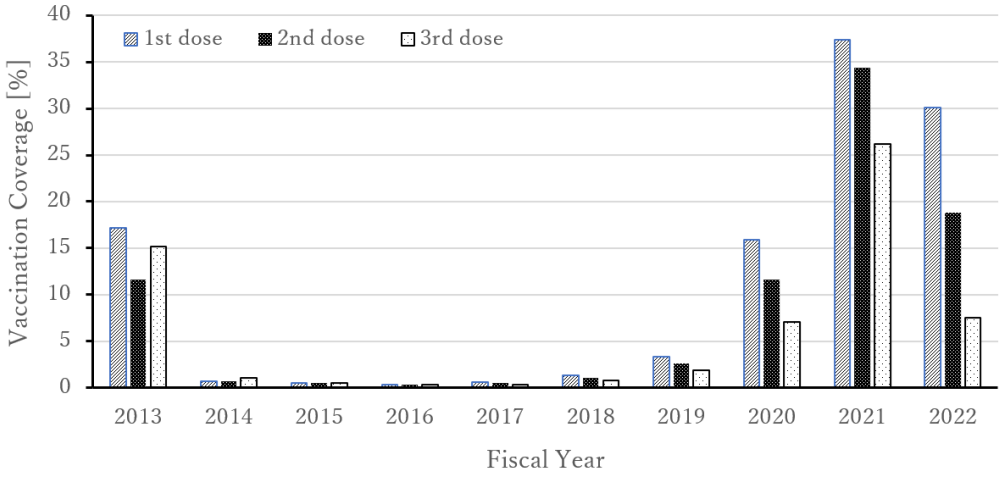


Figure 1. Trends of the human papilloma virus (HPV) vaccine coverage among the target population in Japan. (*Note*: As for 2022, only data from April to September was publicly available.)

July 2020 and resumed recommendations in November 2021. In line with a previous analysis concerning changes in policy defaults that contributed to significant changes in people's behavior (*9*), 30.1% of those eligible for routine HPV vaccination had received at least one vaccination from April 2022, when local governments resumed distribution, to September of the same year. According to government statistics, this is almost double compared to 15.9% in the fiscal year 2020.

Although Japan's HPV vaccine hesitancy is still conspicuous compared to other countries worldwide, the multiplier efforts have supported a recovery trend in the coverage. Also, the increase in COVID-19 vaccination coverage may have contributed to lessening vaccine hesitancy (*10*), resulting in more HPV vaccine coverage among the population. However, the coverage is still far from the sufficient level of 90%, which the World Health Organization has recommended, and continued communication and education about the long-term preventive benefits of the HPV vaccine is essential to achieve optimal coverage.

Funding: None.

Conflict of Interest: Dr. Tanimoto reported personal fees from Medical Network Systems Inc. and Bionics co. ltd., outside the submitted work. No other disclosures were reported.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021; 71:209-249.
2. Canfell K. Towards the global elimination of cervical cancer. Papillomavirus Res. 2019; 8:100170.
3. Yuri Ito. Uterine Cancer. JACR Monograph: Supplement No.2. *http://www.jacr.info/publicication/Pub/m_supp_02/m_supp2_9.pdf* (accessed February 13, 2023). (in Japanese)
4. Kunitoki K, Funato M, Mitsunami M, Kinoshita T, Reich MR. Access to HPV vaccination in Japan: Increasing social trust to regain vaccine confidence. Vaccine. 2021; 39:6104-6110.
5. Ministry of Health, Labor and Welfare. Human papillomavirus infection - cervical cancer and HPV vaccine. *https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou28/index.html* (accessed May 17, 2023). (in Japanese)
6. Imanishi Y, Kinoshita T, Sakamoto M, Ichimiya M, Mitsunami M, Takahashi T, Shigemi D, Song M, Inaba K. Importance of human papillomavirus vaccination leaflets focusing on the safety profile targeted pediatricians in Japan. Vaccine. 2022; 40:5010-5015.
7. Suzuki S, Hosono A. No association between HPV vaccine and reported post-vaccination symptoms in Japanese young women: Results of the Nagoya study. Papillomavirus Res. 2018; 5:96-103.
8. Sakamoto M, Ishizuka R, Ozawa C, Fukuda Y. Health information and COVID-19 vaccination: Beliefs and attitudes among Japanese university students. PLoS One. 2022; 17:e0277435.
9. Mertens S, Herberz M, Hahnel UJJ, Brosch T. The effectiveness of nudging: A meta-analysis of choice architecture interventions across behavioral domains. Proc Natl Acad Sci U S A. 2022; 119:e2107346118.
10. Trujillo KL, Green J, Safarpour A Lazer D, Lin J, Motta M. Covid-19 spillover effects onto general vaccine attitudes. *https://osf.io/w7mq5/* (accessed May 17, 2023).

Received February 13, 2023; Revised May 17, 2023; Accepted May 23, 2023.

Released online in J-STAGE as advance publication May 25, 2023.

§*These authors contributed equally to this work.*
**Address correspondence to*:
Yudai Kaneda, School of Medicine, Hokkaido University, Kita-ku, Kita 15, Nishi 7, Sapporo, Hokkaido 0608638, Japan.
E-mail: nature271828@gmail.com

Global Health & Medicine

1. Scope of Articles

Global Health & Medicine is (Print ISSN 2434-9186, Online ISSN 2434-9194) is an international, open-access, peer-reviewed journal dedicated to publishing high-quality original research that contributes to advancing global health and medicine, with the goal of creating a global information network for global health, basic science as well as clinical science oriented for clinical application.

We encourage submission of original research findings in the fields of global health, public health, and health care delivery as well as the seminal and latest research on the intersection of biomedical science and clinical practice.

2. Types of Articles

Original Articles should be well-documented, novel, and significant to the field as a whole. They should include an abstract and be structured as follows: Title page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgments, References, Figures and/or Tables; and Supplementary Data, if appropriate. Original articles should not exceed 5,000 words in length (excluding references) and should be limited to a maximum of 50 references. Articles may contain a maximum of 10 figures and/or tables. Supplementary Data are permitted but should be limited to information that is not essential to the general understanding of the research presented in the main text, such as unaltered blots and source data as well as other file types.

Types of Articles	Words in length (excluding references)	Figures and/or Tables	References
Original Articles	~5,000	~10	~50
Brief Reports	~3,000	~5	~30
Reviews	~8,000	~10	~100
Mini reviews	~4,000	~5	~50
Policy Forum articles	~3,000	~5	~30
Communications	~2,000	~2	~20
Perspectives			
Comments			
Correspondence			
Editorials	~1,000	~1	~10
Letters	~1,000	~1	~10
News	~800	~1	~5

Abstract: ~250 words (Original Articles, Brief Reports, Reviews, Policy Forum); ~150 words (Communications, Editorials, Letters, and News).
Keywords: 3~6 words

Brief Reports definitively documenting either experimental results or informative clinical observations will be considered for publication in this category. Brief Reports are not intended for publication of incomplete or preliminary findings. Brief Reports should not exceed 3,000 words in length (excluding references) and should be limited to a maximum of 5 figures and/or tables and 30 references. Brief Reports should be structured as follows: Title page, Abstract, Introduction, Materials and Methods, Results and Discussion, Acknowledgments, References, Figures and/or Tables; and Supplementary Data, if appropriate.

Reviews should present a full and up-to-date account of recent developments within an area of research. Normally, reviews should not exceed 8,000 words in length (excluding references) and should be limited to a maximum of 100 references and up to 10 figures and/or tables. Mini reviews are also accepted, which should not exceed 4,000 words in length (excluding references), have no more than 50 references, and have up to 5 figures and/or tables.

Policy Forum articles discuss research and policy issues in areas related to global health and medicine, such as public health, medical care, and social science that may address governmental issues at district, national, and international levels of discourse. Policy Forum articles should not exceed 3,000 words in length (excluding references), have no more than 30 references, and have up to 5 figures and/or tables.

Communications are short, timely pieces that spotlight new research findings or policy issues of interest to the field of global health and medical practice that are of immediate importance. Depending on their content, Communications will be published as "Perspectives", "Comments", or "Correspondence". Communications should not exceed 2,000 words in length (excluding references), have no more than 20 references, and have up to 2 figures and/or tables.

Editorials are short, invited opinion pieces that discuss an issue of immediate importance to the fields of global health, medical practice, and basic science oriented for clinical application. Editorials should not exceed 1,000 words in length (excluding references), have no more than 10 references, and have one figure or table.

Letters are articles that provide readers with an opportunity to respond to an article published in *Global Health & Medicine* within the previous two months or to raise issues of general interest to our readers. Letters should provide new information or insights. If appropriate, letters are sent to the authors of the article in question for a response. Letters should not exceed 1,000 words in length (excluding references), have no more than 10 references, and have one figure or table.

News articles should report the latest events in health sciences and medical research from around the world. News should not exceed 800 words in length (excluding references), have no more than 5 references, and have one figure or table.

3. Formatting Guidelines

Manuscripts should be written in clear, grammatically correct English and submitted as a Microsoft Word file in a single-column format. Manuscripts must be paginated and typed in 12-point Times New Roman font with 24-point line spacing. Please do not embed figures in the text. Technical terms should be defined. Abbreviations should be used as little as possible and should be explained at first mention unless the term is a well-known abbreviation (*e.g.* DNA). Single words should not be abbreviated. Please include page numbers in your submitted file. We also encourage use of line numbers.

The submission to *Global Health & Medicine* should include:

1. Cover letter
2. Main manuscript
3. Figures
4. Supplementary Data, if appropriate

The main manuscripts should be assembled in the following order:

1. Title page
2. Abstract
3. Main Text
4. Acknowledgments
5. References
6. Tables
7. Figure Legend
8. List of Supplementary Data, if appropriate

For manuscript samples, please visit *https://www.globalhealthmedicine.com/site/download.html* (Download Center).

Please provide all figures as separate files in an acceptable format (TIFF

or JPEG). Supplementary Data should also be submitted as a single separate file in Microsoft Word format.

An abstract is necessary for all types of articles. An Original Article should be structured as follows: Title page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgments, References, Figures and/or Tables; and Supplementary Data, if appropriate. A Brief Report contains the same sections as an Original Article, but the Results and Discussion sections should be combined. For manuscripts that are Reviews, Policy Forum articles, Communications, Editorials, Letters, or News, subheadings should be used for increased clarity.

4. Manuscript Preparation

Title page: The title page must include 1) the title of the paper (Please note the title should be short, informative, and contain the major key words); 2) full name(s) and affiliation(s) of the author(s), 3) abbreviated names of the author(s), 4) full name, mailing address, telephone/fax numbers, and e-mail address of the corresponding author; and 5) conflicts of interest (if you have an actual or potential conflict of interest to disclose, it must be included as a footnote on the title page of the manuscript; if no conflict of interest exists for each author, please state "There is no conflict of interest to disclose").

Abstract: The abstract should briefly state the purpose of the study, methods, main findings, and conclusions. For articles that are Original Articles, Brief Reports, Reviews, or Policy Forum articles, a one-paragraph abstract consisting of no more than 250 words must be included in the manuscript. For Communications, Editorials, Letters, and News, a one-paragraph brief summary of the main content in 150 words or less should be included in the manuscript. Abbreviations must be kept to a minimum and non-standard abbreviations should be explained in brackets at first mention. References should be avoided in the abstract. Three to six key words or phrases that do not occur in the title should be included on the Abstract page.

Introduction: The introduction should provide sufficient background information to make the article intelligible to readers in other disciplines and sufficient context clarifying the significance of the experimental findings.

Materials/Patients and Methods: The description should be brief but with sufficient detail to enable others to reproduce the experiments. Procedures that have been published previously should not be described in detail but appropriate references should simply be cited. Only new and significant modifications of previously published procedures require complete description. Names of products and manufacturers with their locations (city and state/country) should be given and sources of animals and cell lines should always be indicated. All clinical investigations must have been conducted in accordance with the Declaration of Helsinki (as revised in 2013, *https://wma.net/what-we-do/medical-ethics/declaration-of-helsinki*). All human and animal studies must have been approved by the appropriate institutional review board(s) and a specific declaration of approval must be made within this section.

Results: The description of the experimental results should be succinct but in sufficient detail to allow the experiments to be analyzed and interpreted by an independent reader. If necessary, subheadings may be used for an orderly presentation. Two levels of subheadings may be used if warranted, please distinguish them clearly. All Figures and Tables should be cited in order, including those in the Supplementary Data.

Discussion: The data should be interpreted concisely without repeating material already presented in the Results section. Speculation is permissible, but it must be well-founded, and discussion of the wider implications of the findings is encouraged. Conclusions derived from the study should be included in this section.

Acknowledgments: All funding sources should be credited in the Acknowledgments section. In addition, people who contributed to the work but who do not meet the criteria for authors should be listed along with their contributions.

References: References should be numbered in the order in which they appear in the text. Two references are cited separated by a comma, with no space, for example (*1,2*). Three or more consecutive references are given as a range with an en rule, for example (*1-3*). Citing of unpublished results, personal communications, conference abstracts, and theses in the reference list is not recommended but these sources may be mentioned in the text. In the reference list, cite the names of all authors when there are fifteen or fewer authors; if there are sixteen or more authors, list the first three followed by *et al*. Names of journals should be abbreviated in the style used in PubMed. Authors are responsible for the accuracy of the references. The EndNote Style of *Global Health & Medicine* could be downloaded at Download Center.

Examples are given below:

Example 1 (Sample journal reference):
Kokudo N, Hara T. "History, Tradition, and Progress": The ceremony of 150th Anniversary of the National Center for Global Health and Medicine held in Tokyo, Japan. BioSci Trends. 2019; 13:105-106.

Example 2 (Sample journal reference with more than 15 authors):
Darby S, Hill D, Auvinen A, *et al*. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. BMJ. 2005; 330:223.

Example 3 (Sample book reference):
Shalev AY. Post-traumatic stress disorder: Diagnosis, history and life course. In: Post-traumatic Stress Disorder, Diagnosis, Management and Treatment (Nutt DJ, Davidson JR, Zohar J, eds.). Martin Dunitz, London, UK, 2000; pp. 1-15.

Example 4 (Sample web page reference):
World Health Organization. The World Health Report 2008 – primary health care: Now more than ever. *http://www.who.int/whr/2008/whr08_en.pdf* (accessed March 20, 2022).

Tables: All tables should be prepared in Microsoft Word and should be arranged at the end of the manuscript after the References section. Please note that tables should not be in image format. All tables should have a concise title and should be numbered consecutively with Arabic numerals. Every vertical column should have a heading, consisting of a title with the unit of measure in parentheses. If necessary, additional information should be given below the table.

Figure Legend: The figure legend should be typed on a separate page of the main manuscript and should include a short title and explanation. The legend should be concise but comprehensive and should be understood without referring to the text. Symbols used in figures must be explained. Any individually labeled figure parts or panels (A, B, *etc*.) should be specifically described by part name within the legend.

Figure Preparation: All figures should be clear and cited in numerical order in the text. Figures must fit in a one- or two-column format on the journal page: 8.3 cm (3.3 in.) wide for a single column, 17.3 cm (6.8 in.) wide for a double column; maximum height: 24.0 cm (9.5 in.). Please make sure that the symbols and numbers appearing in the figures are clear. Please make sure that artwork files are in an acceptable format (TIFF or JPEG) at minimum resolution (600 dpi for illustrations, graphs, and annotated artwork, and 300 dpi for micrographs and photographs). Please provide all figures as separate files. Please note that low-resolution images are one of the leading causes of article resubmission and scheduling delays.

Units and Symbols: Units and symbols conforming to the International System of Units (SI) should be used for physicochemical quantities. Solidus notation (*e.g*. mg/kg, mg/mL, mol/mm^2/min) should be used. Please refer to the SI Guide www.bipm.org/en/si/ for standard units.

Supplemental Data: Supplemental data might help to support and enhance your manuscript. *Global Health & Medicine* accepts the submission of these materials, which will be only published online alongside the electronic version of your article. Supplemental files (figures, tables, and other text materials) should be prepared according to the above guidelines, numbered in Arabic numerals (*e.g.*, Figure S1, Figure S2, and Table S1, Table S2), and referred to in the text. All figures and tables should have titles and legends. All figure legends, tables and supplemental text materials should be placed at the end of the paper. Please note all of these supplemental data should be provided at the time of initial submission and note that the editors reserve the right to limit the size and length of Supplemental Data.

5. Cover Letter

The manuscript must be accompanied by a cover letter prepared by the corresponding author on behalf of all authors. The letter should indicate the basic findings of the work and their significance. The letter should also include a statement affirming that all authors concur with the submission and that the material submitted for publication has not been published previously or is not under consideration for publication elsewhere. For example of Cover Letter, please visit *https://www.globalhealthmedicine.com/site/download.html* (Download Center).

6. Submission Checklist

The Submission Checklist will be useful during the final checking of a manuscript prior to sending it to Global Health & Medicine for review. Please visit *https://www.globalhealthmedicine.com/site/download.html* and download the Submission Checklist file.

7. Online Submission

Manuscripts should be submitted to *Global Health & Medicine* online at *https://www.globalhealthmedicine.com/site/login.html*. Receipt of your manuscripts submitted online will be acknowledged by an e-mail from Editorial Office containing a reference number, which should be used in all future communications. If for any reason you are unable to submit a file online, please contact the Editorial Office by e-mail at *office@globalhealthmedicine.com*

8. Editorial Policies

For publishing and ethical standards, *Global Health & Medicine* follows the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals issued by the International Committee of Medical Journal Editors (ICMJE, *https://icmje.org/recommendations*), and the Principles of Transparency and Best Practice in Scholarly Publishing jointly issued by the Committee on Publication Ethics (COPE, *https://publicationethics.org/resources/guidelines-new/principles-transparency-and-best-practice-scholarly-publishing*), the Directory of Open Access Journals (DOAJ, *https://doaj.org/apply/transparency*), the Open Access Scholarly Publishers Association (OASPA, *https://oaspa.org/principles-of-transparency-and-best-practice-in-scholarly-publishing-4*), and the World Association of Medical Editors (WAME, *https://wame.org/principles-of-transparency-and-best-practice-in-scholarly-publishing*).

Global Health & Medicine will perform an especially prompt review to encourage submissions of innovative work. All original research manuscripts are to be subjected to an expeditious but rigorous standard of peer review, and are to be edited by experienced copy editors to the highest standards.

The publishing is supported by the International Research and Cooperation Association for Bio & Socio-Sciences Advancement (IRCA-BSSA) Group Journals. The editorial office comprises a range of experienced individuals, including managing editor, editorial associates, software specialists, and administrative coordinators to provide a smooth service for authors and reviewers.

Ethical Approval of Studies and Informed Consent: For all manuscripts reporting data from studies involving human participants or animals, formal review and approval, or formal review and waiver, by an appropriate institutional review board or ethics committee is required and should be described in the Methods section. When your manuscript contains any case details, personal information and/or images of patients or other individuals, authors must obtain appropriate written consent, permission, and release in order to comply with all applicable laws and regulations concerning privacy and/or security of personal information. The consent form needs to comply with the relevant legal requirements of your particular jurisdiction, and please do not send the signed consent form to *Global Health & Medicine* in order to respect your patient's and any other individual's privacy. Please instead describe the information clearly in the Methods (patient consent) section of your manuscript while retaining copies of the signed forms in the event they should be needed. Authors should also state that the study conformed to the provisions of the Declaration of Helsinki (as revised in 2013, *https://wma.net/what-we-do/medical-ethics/declaration-of-helsinki*). When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

Reporting Clinical Trials: The ICMJE (*https:// icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html*) defines a clinical trial as any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the relationship between a health-related intervention and a health outcome. Registration of clinical trials in a public trial registry at or before the time of first patient enrollment is a condition of consideration for publication in *Global Health & Medicine*, and the trial registration number will be published at the end of the Abstract. The registry must be independent of for-profit interest and be publicly accessible. Reports of trials must conform to CONSORT 2010 guidelines (*https://consort-statement.org/consort-2010*). Articles reporting the results of randomized trials must include the CONSORT flow diagram showing the progress of patients throughout the trial.

Conflict of Interest: All authors are required to disclose any actual or potential conflict of interest, including financial interests or relationships with other people or organizations that might raise questions of bias in the work reported. If no conflict of interest exists for each author, please state "There is no conflict of interest to disclose".

Submission Declaration: When a manuscript is considered for submission to *Global Health & Medicine*, the authors should confirm that 1) no part of this manuscript is currently under consideration for publication elsewhere; 2) this manuscript does not contain the same information in whole or in part in manuscripts that have been published, accepted, or are under review elsewhere, except in the form of an abstract, a letter to the editor, or part of a published lecture or academic thesis; 3) authorization for publication has been obtained from the authors' employer or institution; and 4) all contributing authors have agreed to submit this manuscript.

Initial Editorial Check: Immediately after submission, the journal's managing editor will perform an initial check of the manuscript. A suitable academic editor will be notified of the submission and invited to check the manuscript and recommend reviewers. Academic editors will check for plagiarism and duplicate publication at this stage. The journal has a formal recusal process in place to help manage potential conflicts of interest of editors. In the event that an editor has a conflict of interest with a submitted manuscript or with the authors, the manuscript, review, and editorial decisions are managed by another designated editor without a conflict of interest related to the manuscript.

Peer Review: *Global Health & Medicine* operates a single-anonymized review process, which means that reviewers know the names of the authors, but the authors do not know who reviewed their manuscript. All articles are evaluated objectively based on academic

content. External peer review of research articles is performed by at least two reviewers, and sometimes the opinions of more reviewers are sought. Peer reviewers are selected based on their expertise and ability to provide quality, constructive, and fair reviews. For research manuscripts, the editors may, in addition, seek the opinion of a statistical reviewer. Every reviewer is expected to evaluate the manuscript in a timely, transparent, and ethical manner, following the COPE guidelines (*https://publicationethics.org/files/cope-ethical-guidelines-peer-reviewers-v2_0.pdf*). We ask authors for sufficient revisions (with a second round of peer review, when necessary) before a final decision is made. Consideration for publication is based on the article's originality, novelty, and scientific soundness, and the appropriateness of its analysis.

Suggested Reviewers: A list of up to 3 reviewers who are qualified to assess the scientific merit of the study is welcomed. Reviewer information including names, affiliations, addresses, and e-mail addresses should be provided at the same time the manuscript is submitted online. Please do not suggest reviewers with known conflicts of interest, including participants or anyone with a stake in the proposed research; anyone from the same institution; former students, advisors, or research collaborators (within the last three years); or close personal contacts. Please note that the Editor-in-Chief may accept one or more of the proposed reviewers or request a review by other qualified persons.

Submission Turnaround Time:

- From submission to first editorial decision: 1-2 weeks.
- From acceptance to publication ahead of print: 1-4 weeks.
- From acceptance to publication: 2-6 months. Original Articles are listed as priority.

Language Editing: Manuscripts prepared by authors whose native language is not English should have their work proofread by a native English speaker before submission. If not, this might delay the publication of your manuscript in *Global Health & Medicine*.

Copyright and Reuse: Before a manuscript is accepted for publication in *Global Health & Medicine*, authors will be asked to sign a transfer of copyright agreement, which recognizes the common interest that both the journal and author(s) have in the protection of copyright. We accept that some authors (*e.g.*, government employees in some countries) are unable to transfer copyright. A JOURNAL PUBLISHING AGREEMENT (JPA) form will be e-mailed to the authors by the Editorial Office and must be returned by the authors by mail, fax, or as a scan. Only forms with a hand-written signature from the corresponding author are accepted. This copyright will ensure the widest possible dissemination of information. Please note that the manuscript will not proceed to the next step in publication until the JPA Form is received. In addition, if excerpts from other copyrighted works are included, the author(s) must obtain written permission from the copyright owners and credit the source(s) in the article.

9. Accepted Manuscripts

Proofs: Galley proofs in PDF format will be e-mailed to the corresponding author. Corrections must be returned to the editor (*office@globalhealthmedicine.com*) within 3 working days.

Offprints: Authors will be provided with electronic offprints of their article. Paper offprints can be ordered at prices quoted on the order form that accompanies the proofs.

Article-processing Charges: The open-access policy of *Global Health & Medicine* will allow all readers from the medical and scientific community to freely utilize material published in the journal. To achieve open access, article-processing charges ($150 per page for black & white pages, $300 per page for color pages) will be levied for manuscripts accepted for publication in *Global Health & Medicine*. In exceptional circumstances, the author(s) may apply to the editorial office for a waiver of the publication charges at the time of submission. All invited articles are free of charge.

Article-processing charges pay for: Immediate, worldwide open access to the full article text; Preparation in various formats for print & online publication; Inclusion in global important platforms, enabling electronic citation in other journals that are available electronically.

Misconduct: *Global Health & Medicine* takes seriously all allegations of potential misconduct and adhere to the ICMJE Guideline (*https://icmje.org/recommendations*) and COPE Guideline (*https://publicationethics.org/files/Code_of_conduct_for_journal_editors.pdf*). In cases of suspected research or publication misconduct, it may be necessary for the Editor or Publisher to contact and share submission details with third parties including authors' institutions and ethics committees. The corrections, retractions, or editorial expressions of concern will be performed in line with above guidelines.

(*As of November 2022*)

Global Health & Medicine
National Center for Global Health and Medicine,
1-21-1 Toyama Shinjuku-ku, Tokyo 162-8655, Japan
URL: *www.globalhealthmedicine.com*
E-mail: *office@globalhealthmedicine.com*

Print ISSN: 2434-9186 Online ISSN: 2434-9194

NCGM

GHM

Global Health & Medicine

Volume 1, Number 1
October, 2019

www.globalhealthmedicine.com