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

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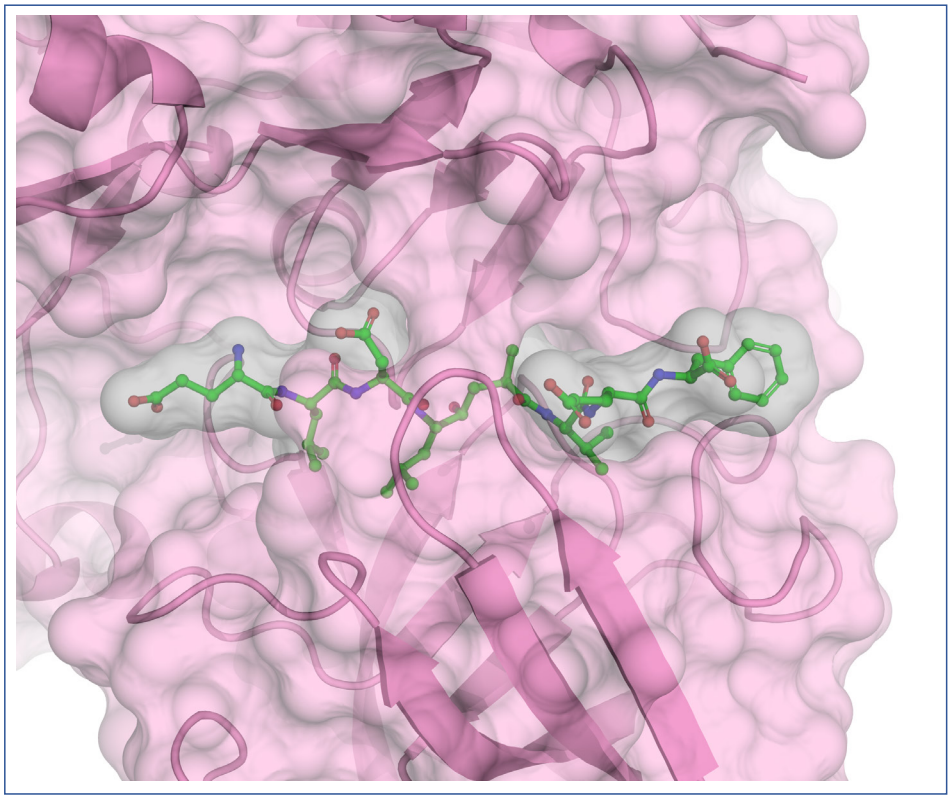
Global Health & Medicine

Volume 6, Number 3
June, 2024



Surface and cartoon representation of BACE1 (β-site amyloid precursor protein cleaving enzyme 1) complexed with inhibitor OM00-3 (*see the back of the cover and Editorial*)

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

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Global Health & Medicine

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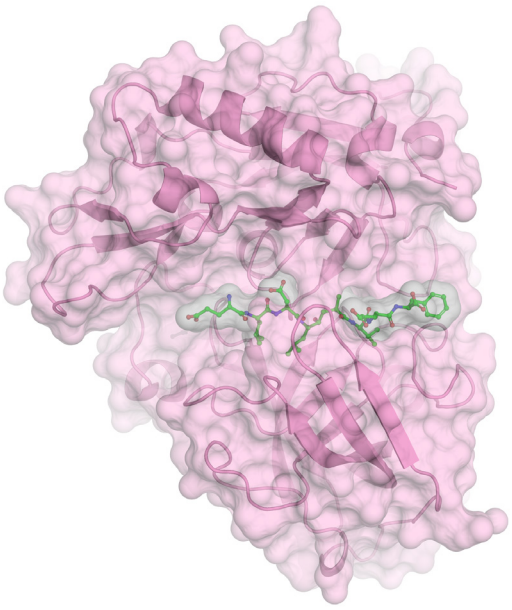

Surface and cartoon representation of BACE1 (β-site amyloid precursor protein cleaving enzyme 1) is shown in pink (PDB code: 1M4H), in complex with inhibitor OM00-3 shown in yellow. The OM00-3 inhibitor consists of the sequence Glu-Leu-Asp-Leu*Ala-Val-Glu-Phe, where the asterisk (*) denotes the hydroxy ethylene transition state isostere and has a Ki value of 0.3 nM. The OM99-2 and OM00-3 were developed in the early 2000s to target BACE1 activity to reduce Aβ peptide accumulation in the brain, aiming to treat Alzheimer's disease. (By *Haydar Bulut* and *Arun K Ghosh*)

Global Health & Medicine. 2024; 6(3):164-169.

EDITORIAL

DOI: 10.35772/ghm.2024.01033

BACE1 inhibitor drugs for the treatment of Alzheimer's disease: Lessons learned, challenges to overcome, and future prospects†

Arun K. Ghosh[1,2,*]

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

Abstract: Alzheimer's disease (AD), first diagnosed over a century ago, remains one of the major healthcare crises around the globe. Currently, there is no cure or effective treatment. The majority of drug development efforts to date have targeted reduction of amyloid-β peptide (Aβ). Drug development through inhibition of beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), resulted in promising early clinical studies. However, nearly all small molecule BACE1 inhibitor drugs failed to live up to expectations in later phase clinical trials, due to toxicity and efficacy issues. This commentary aims to provide a brief review of over two decades of BACE1 inhibitor drug development challenges and efforts for treatment of AD and prospects of future BACE1-based drugs.

***Keywords*:** Alzheimer disease, amyloid, BACE1, inhibitor, drug development

Alzheimer's disease (AD) is a neurodegenerative disorder in the brain that leads to progressive impairment of cognition and memory loss (*1*). AD mostly affects elderly patients and there are over 55 million individuals diagnosed with AD around the globe. Currently, there is no cure or disease-modifying treatment (*2*). Thus far, the majority of approved drugs may help to manage symptoms of the disease. The hallmark of AD is the accumulation of neurotoxic amyloid-β peptides (Aβ), mainly Aβ40 and Aβ42, in the brain which is considered a pivotal feature of AD pathogenesis. Among numerous hypotheses explaining the mechanisms underlying AD pathogenesis, the "Amyloid Cascade Hypothesis" introduced in the 1990's remains one of the most widely studied conceptual frameworks for AD drug development (*3,4*). The β-site amyloid precursor protein cleaving enzyme 1 (BACE1) was cloned and identified over two decades ago (*5,6*). The prospect of developing anti-amyloid-β drugs generated huge enthusiasm and anticipation at that time. This initial excitement is understandable as BACE1 is the first protease that initiates production of Aβ in the brain by cleaving the amyloid precursor protein (APP) and forming a soluble *N*-terminal fragment and amyloid-β peptide containing a membrane anchored *C*-terminal fragment (Figure 1). In the following step, γ-secretase cleaves the *C*-terminal fragment, releasing the neurotoxic Aβ peptides of different lengths. Among these, Aβ42 has been recognized as the major cause for onset and progression of AD. Logically, both proteases became important drug development targets against AD. Several γ-secretase inhibitor drug candidates were brought to clinical trials, however they were associated with high toxicity and major side effects. The toxicity appears to be mechanism-based because γ-secretase plays an important role in maintaining important physiological functions (*7*). Since BACE1 is involved in the first step of Aβ production, inhibition of BACE1 was thought to avoid the late stages of AD pathogenesis and issues associated with function-based problems of γ-secretase. However, BACE1 has been shown to process other substrates, which set up potential new challenges (*8,9*).

The design of the first substrate-based potent BACE1 inhibitor, OM99-2, and subsequent determination of the X-ray crystal structure of OM99-2 bound BACE1 was reported in 2000 (Figure 2) (*10,11*). This development set the stage for structure-based evolution of potent and drug-like BACE1 inhibitors. The overall medicinal chemistry development is nothing short of astounding. Today, there are over 250 X-ray crystal structures of BACE1 and inhibitor complexes in the protein database. Also, there exists a large number of patents with many different structural classes (*12,13*). For BACE1 inhibitor clinical development, the challenging problems are to develop drug-like molecules with good selectivity against BACE2 and other aspartic acid proteases. Ideally, such BACE1 inhibitor drugs need to be smaller, have less peptidic features, have efficient blood-brain-barrier penetration, and reduced susceptibility to Pgp-mediated efflux (*14*).

The early development of peptidomimetic small molecule BACE1 inhibitors containing classical

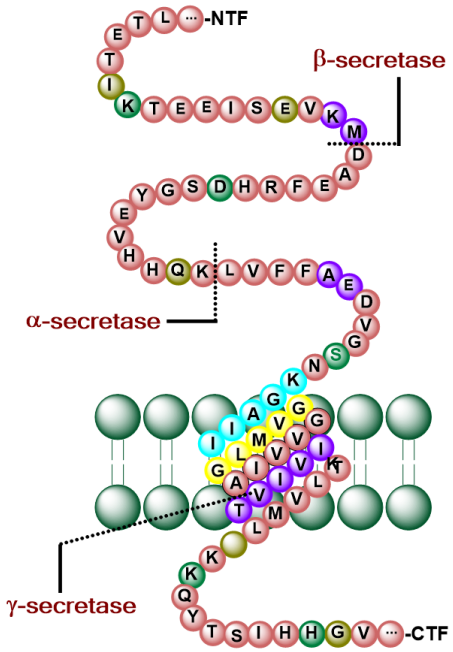

Figure 1. APP cleavage by β- and γ-secretases, common APP mutations in purple. APP, amyloid precursor protein.

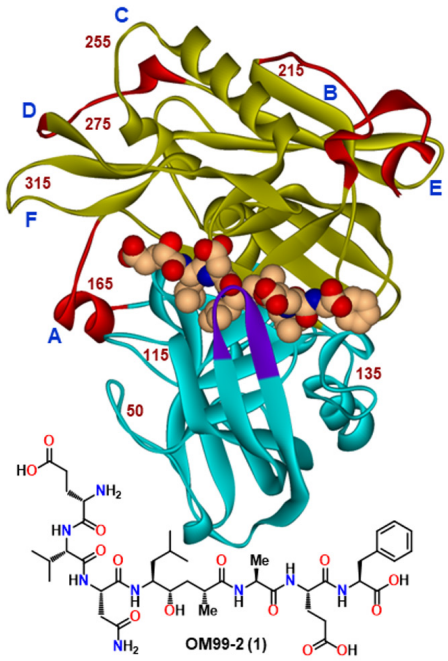

Figure 2. BACE1 inhibitor OM99-2 and Xray structure of BACE1-OM99-2 complex (pdb:1FKN). BACE1, beta-site amyloid precursor protein cleaving enzyme 1.

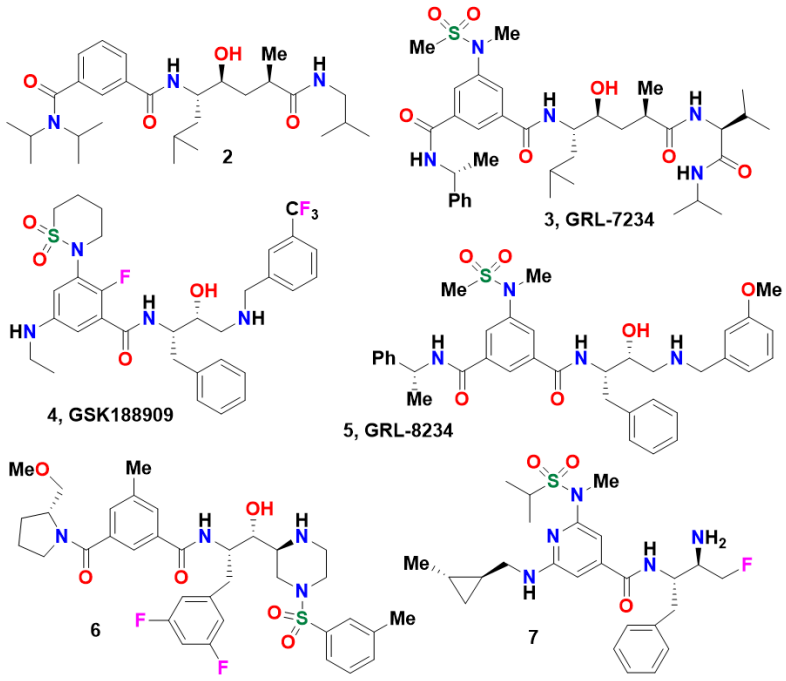

Figure 3. Early evolution of drug-like BACE1 inhibitors with classical dipeptide isosteres. BACE1, beta-site amyloid precursor protein cleaving enzyme 1.

dipeptide isosteres is highlighted in Figure 3. Small molecule BACE1 inhibitor **2** with the Leu-Ala isostere showed good potency IC_{50} = 30 nM, EC_{50}= 3 μM, HEK-293) and cell penetration (*15*). Compound **3** displayed potent BACE1 activity as well as cellular activity (K_i = 1.1 nM, cell EC_{50} = 39 nM). It also showed over 25-fold selectivity against BACE2 and cathepsin D (*16*). Inhibitor **4** with a hydroxy ethylamine isostere (GSK 188909, IC_{50} = 4 nM, cell EC_{50} = 5 nM) showed good selectivity over other aspartic acid proteases and lowered Aβ in transgenic mice (*17*). Inhibitor **5** displayed potent BACE1 activity (K_i = 1.8 nM, cell EC_{50} = 1 nM), modest selectivity against BACE2 and cathepsin D (IC_{50} = 79 nM and 138 nM, respectively), and showed inhibition of Aβ production in transgenic mice (*18*). Intraperitoneal administration of compound **5** with an 8 mg/kg dose

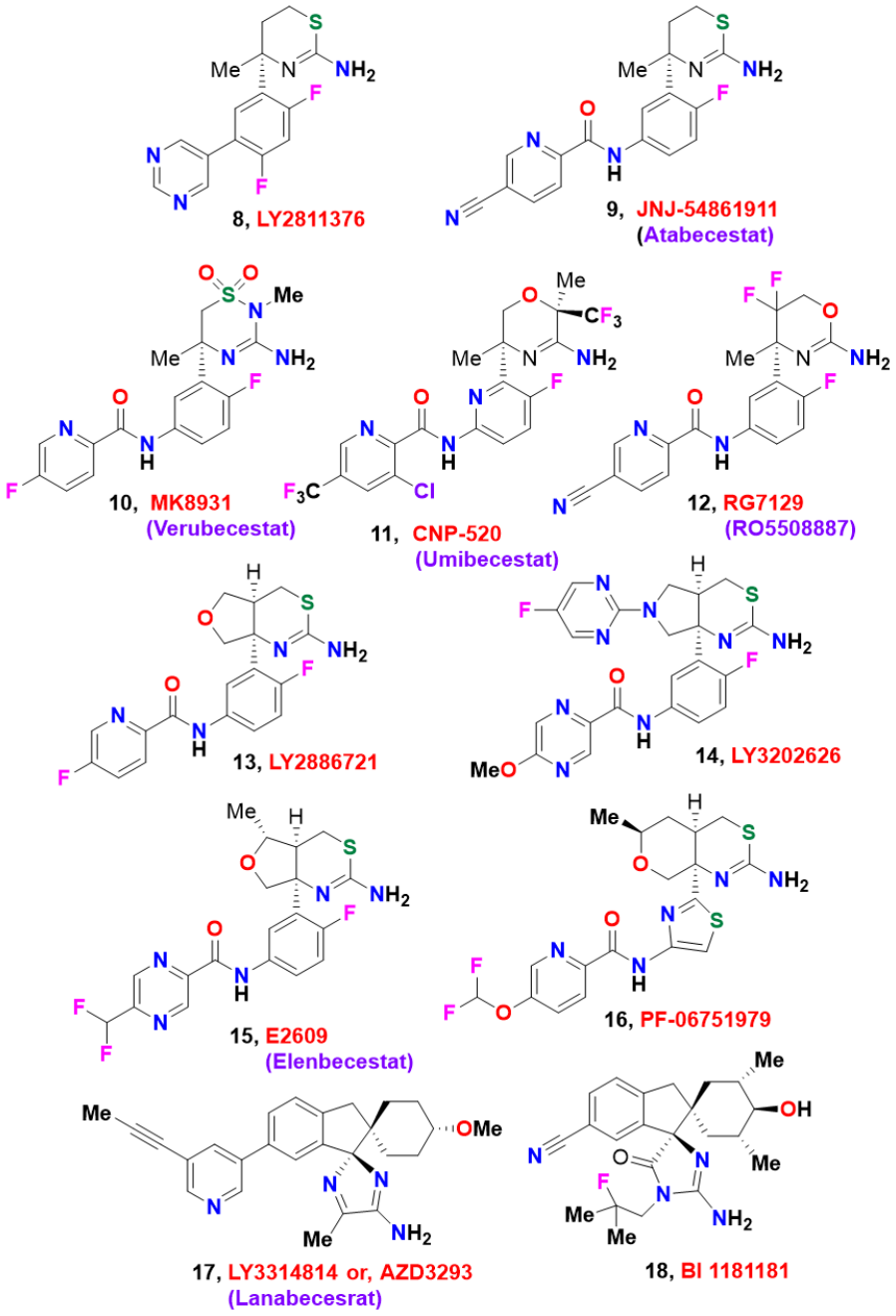

Figure 4. Nonpeptide small molecule BACE1 inhibitors developed for clinical trials. BACE1, beta-site amyloid precursor protein cleaving enzyme 1.

to Tg2579 mice showed 65% reduction of plasma Aβ production after 3 h. Furthermore, this compound has been shown to rescue age-related cognitive decline in transgenic mice. Piperazine derivative **6** was developed as a potent BACE1 inhibitor (IC_{50} = 0.18 nM, cell EC_{50} = 7 nM) (*19,20*). This compound was shown to inhibit peripheral $A\beta_{40}$ in transgenic mice with a single dose. Compound **7** displayed potent *in vitro* activity (cell IC_{50} = 49 nM) and exhibited an *in vitro* $A\beta_{40}$ reduction of 34% in transgenic mice after 3 h using a 50 mg/kg dose (*21*). Also, it showed good drug concentration in the brain (1.9 μM).

To date, no BACE1 inhibitor drug is approved by the FDA. However, fourteen BACE1 inhibitor drugs were evaluated in clinical trials (*13,22*). CTS21166 was the first BACE1 inhibitor reported to have undergone a phase I clinical trial, showing oral bioavailability, CSF penetration, metabolic stability and toxicology profiles. For healthy volunteers receiving 225 mg IV or 200 mg oral doses, CTS21166 exhibited Aβ40 reduction up to 80% in 4-8 h with sustained reduction up to 72 h and showed 40% oral bioavailability in humans. Chemical structure and other information regarding further clinical studies were not reported (*23,24*). Despite steady progress towards drug-like peptidomimetic BACE1 inhibitors, the development of nonpeptide

small molecule heterocyclic BACE1 inhibitors was also pursued. Various high-throughput screening and fragment-based screening of scaffolds were utilized to discover new structural classes that have no peptide features, good metabolic stabilities, and better blood-brain barrier (BBB) penetration ability. These efforts led to the identification of several structural leads which upon medicinal chemistry optimization resulted in the development of potent BACE1 inhibitors with promising pharmacological properties. Several of these BACE1 inhibitors were advanced to clinical development and phase I-III clinical trials were conducted from 2012-2019 (*13,14*). These compound structures are highlighted in Figure 4. One of the interesting features of these clinical agents is the presence of a cyclic amidine functionality. The X-ray structural analysis of BACE1 and inhibitor complexes revealed that the core amidine functionality forms a network of hydrogen bonds with the catalytic aspartates in flap-open conformation of the BACE1. The adjacent fluorobenzene scaffold fills the S1-S2 subsites while the substituted heterocyclic amide derivatives occupy the S3 subsite. Compounds **8**, **9**, **13-16** contain amino-thiazine structural features, compounds **11** and **12** possess amino-oxazine scaffolds while candidates **10** and **18** contain a cyclic guanidine core which interacts with the catalytic aspartate of BACE1. In general, these compounds showed acceptable ADME properties in laboratory animals. In phase I clinical trials, most of these compounds exhibited general tolerability, acceptable safety profiles, BBB penetration, and decline of Aβ levels in CSF. Compound **8** (LY2811376) completed a phase I clinical trial but was discontinued due to toxicological issues. The development of compound **9** (LY2886721) was terminated after phase I and II clinical trials due to abnormal liver enzyme elevation for a number of patients. From 2014-2019, several compounds advanced to phase II and phase III clinical trials with early AD patients. Clinical development of all BACE1 inhibitors, including JNJ-54861911 (**9**), MK-8931(**10**), CNP-520 (**11**), E2609 (**15**) and LY3314814 (**17**), was terminated because the treatment did not exhibit clinical benefit, slow disease progression, nor slow down cognitive decline, and in some cases caused cognitive worsening (*22,25*).

All BACE1 inhibitor Alzheimer's disease clinical trials have been terminated at present; however, this is not the end of BACE drug development. BACE1 remains one of the most promising drug targets for decelerating Aβ production and intervention of AD pathophysiology. Despite major setbacks, the BACE inhibitor clinical trials provided a lot of useful knowledge and a wealth of scientific information for future directions. It is time to scrutinize data, critically analyze pitfalls, and apply the lessons learned toward successful BACE drug development. Many past Alzheimer's drug trials dealt with uncertainties and failures, particularly in the development of immunotherapies. After many obstacles, more recent trials with amyloid reducing-antibodies have been shown to slow down AD progression by targeting fibrillar and pre-fibrillar forms of amyloid aggregates. The recent FDA approval of lecanemab for slowing progression of mild cognitive impairment in early AD patients supports the amyloid hypothesis (*26,27*). BACE1 inhibition in essence provides a complementary pathway by blocking Aβ generation, which ultimately contributes to neurotoxicity and neurodegeneration.

Like the early clinical setbacks with antibody therapies, the early BACE inhibitor drug development efforts also faced numerous concerns including liver toxicity and retinal damage during clinical development. Most recent clinical candidates resolved these issues and compounds with good ADME, BBB properties, and safety profiles have been developed. However, clinical trials presented a new set of problems as these compounds showed no clinical efficacy, undesired side effects, and sometimes cognitive worsening. Are these problems related to BACE1 as a drug target or are they compound specific due to off-target effects? These are important questions that need to be addressed. BACE has two isoforms, BACE1 and BACE2. While BACE2 expression is low in the CNS, its inhibition has been suggested to affect cognition. Also, it is known that BACE processes many other important substrates in the brain, including seizure protein 6, aka sez6-like, neuregulin and NCAML1. Prolonged inhibition of BACE is likely to interfere with structural synaptic plasticity possibly due to diminished processing of sez6 causing disruption of dendritic spine plasticity. Many experts in the field believe a detailed understanding of these BACE1 substrates as well as the physiological role of BACE2 requires further evaluation and understanding (*25,28*). Furthermore, BACE clinical trials resulted in greater than 50% Aβ reduction. Such dramatic reduction may have also contributed towards undesired side effects. Lower doses are likely to reduce side effects. If a low dose reduces Aβ production to a low percentage and slows down the AD onset for a few years, still that would be a significant clinical achievement.

Interestingly, all recent clinical BACE inhibitors showed only marginal selectivity against these two BACE isoforms. It is possible that the lack of selectivity may have contributed to some of the observed side effects. Also, most of the clinical candidates belong to the same structural class as they possess some core similarities, particularly the presence of a cyclic amidine as well as the P1-P2 fluorobenzene scaffold as can be seen in Figure 4. Thus, medicinal chemistry development of structurally more diverse and highly selective BACE1 inhibitors may shed light on BACE1 as a drug target as well as off-target effects related to specific features of compounds. Successful development and use of aspartic acid protease inhibitor drugs has been

accomplished for the treatment of other ailments. It is relevant that approved protease inhibitor drugs for HIV/AIDS and renin inhibitors for treatment of hypertension contain classical hydroxyethylene or hydroxyethylamine dipeptide isosteres at the active site. These drugs have been used for decades as chronic therapies. Since the early development of highly selective BACE1 inhibitors with desirable safety and efficacy in animals has been demonstrated, it may also be appropriate to develop the next generation of selective BACE1 inhibitors utilizing these time-tested classical dipeptide isosteres. These approaches are currently under development and show promise toward highly selective BACE1 inhibitors for disease-modifying treatment of AD. We strongly believe that it is too early to give up on the challenges of the BACE1 target.

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

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

† In memory of Dr. Jordan Tang, a brilliant pioneer and scholar with a kind heart.

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Received May 21, 2024; Accepted June 4, 2024.

Released online in J-STAGE as advance publication June 6, 2024.

**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. 2024; 6(3):170-173.
EDITORIAL
DOI: 10.35772/ghm.2024.01002

Role of liver resection in the era of advanced systemic therapy for hepatocellular carcinoma

Norihiro Kokudo*, Takashi Kokudo, Peipei Song, Wei Tang

National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: The recent dramatic progress in systemic therapy for hepatocellular carcinoma (HCC) provides the possibility of a combination of surgery and systemic therapy including adjuvant, neoadjuvant, or conversion settings. Since the turn of the century, at least three negative studies have tested adjuvant therapies after curative resection or ablation, including uracil-tegafur, which is an oral chemotherapeutic drug, sorafenib, and peretinoin, which a synthetic retinoid that may induce the apoptosis and differentiation of liver cancer cells. Using more potent immuno-checkpoint inhibitors (ICIs), at least 4 phase III trials of adjuvant immunotherapy are ongoing: nivolumab, durvalumab/bevacizumab, pembrolizumab, and atezolizumab+bevacizumab. Very recently, the last trial indicated a significantly better recurrence-free survival (RFS) for adjuvant atezolizumab+bevacizumab. Another promising combination of surgery and systemic therapy is neoadjuvant therapy for potentially resectable cases or a conversion strategy for oncologically unresectable cases. There are 2 neoadjuvant trials for technically or oncologically unresectable HCCs ongoing in Japan: the LENS-HCC trial using lenvatinib and the RACB study using atezolizumab+bevacizumab. A longer follow-up may be needed, but the overall survival (OS) in resected cases seems much higher than that in unresectable cases. Recently, the Japan Liver Cancer Association (JLCA) and the Japanese Society of HPB Surgery (JSHPBS) created a joint working group on "so-called borderline resectable HCC". They obtained a Japanese consensus on this issue that has been published on the websites of JLCA and JSHPBS. The definition of resectability or borderline resectability provides a common language regarding advanced HCC for investigators and is a useful tool for future clinical trials.

***Keywords*:** hepatocellular carcinoma (HCC), adjuvant systemic therapy, neoadjuvant systemic therapy, conversion strategy

As of January 2023, the Food and Drug Administration (FDA) has approved nivolumab, pembrolizumab, ramucirumab, nivolumab/ipilimumab, atezolizumab/bevacizumab, and tremelimumab/durvalumab as first- or second-line monoclonal antibodies (mAbs) for unresectable hepatocellular carcinoma (HCC) in the USA (*1*). In Japan, atezolizumab/bevacizumab was approved in 2020, and it became the regimen of choice for first-line treatment. Durvalumab/tremelimumab was approved as first-line treatment in 2023. In total, 6 or 7 regimens are available for HCC in Japan as of January 2024. The recent dramatic progress in systemic therapy for HCC provides the possibility of a combination of surgery and systemic therapy; *i.e.*, adjuvant, neoadjuvant, or conversion settings.

Adjuvant systemic therapy

The first type of combination is the adjuvant setting: systemic therapy after liver resection. Tumor recurrence is known to be very common even after curative liver resection. The reported 5-yr recurrence rate was as high as 70 to 80% (*2*). There are two peaks for recurrence-free survival (RFS) hazard after liver resection. The first peak is recurrence because of residual micro metastases. The second peak may be because of so-called multi-centric carcinogenesis. Adjuvant therapy is targeted to lower the first wave of recurrence.

There have been several trials on adjuvant therapy to solve this issue. Takayama's adaptive immunotherapy was probably one of the oldest and milestone studies which indicated the impact of adaptive immunotherapy as reported by the National Cancer Center Japan (*3*). They used autologous lymphocytes activated *in vitro* with recombinant interleukin-2 and antibodies against CD3. After culturing for two weeks, they obtained enough T cells with CD3, 4, and 8 markers. The primary endpoint was met, and this immunotherapy significantly reduced the risk of tumor recurrence after resection. However, this adjuvant therapy was not feasible in daily practice

because of the complex procedure for cell preparation and probably the cost. After this study, there have been at least three studies that tested adjuvant therapies after curative resection or ablation, including uracil-tegafur (UFT), which is an oral chemotherapeutic drug (*4*), sorafenib (*5*), and peretinoin, which is a synthetic retinoid that may induce the apoptosis and differentiation of liver cancer cells (*6,7*). All of the subsequent studies were negative in reducing tumor recurrence (*8*).

In the uracil-tegafur study, RFS curves of the UFT arm and control were almost identical. However, overall survival looked even worse in the UFT arm, with a *p*-value of 0.08. As a result, UFT was not recommended as an adjuvant therapy after curative resection (*4*). Subjects of the STORM trial were patients with a moderate risk of recurrence. Sorafenib was administered for as long as 4 years in the experimental arm. Both RFS and overall survival (OS) curves were almost overlapping, and the study was negative. A point worth noting is that the 5-yr OS was as high as 70% even for the placebo arm (*5*).

There are several reasons why most of the previous adjuvant trials for HCC failed. First, defining optimal patient populations was difficult. The outcome of the control arm has been generally too good in previous studies, and there have been no biomarkers for patient selection. Second, there is no set duration for adjuvant therapy. Figure 1A compares the duration among the previous studies and ongoing studies using immuno-checkpoint inhibitors (ICIs). Of note, there is no set duration for this setting. This is probably because peaks in the hazard curve for recurrence are not very steep compared to those for other cancer types (*2*). Severe adverse events (AE) are not acceptable for seemingly healthy patients after curative treatment. Finally, previous studies might have simply indicated insufficient efficacy.

Since the introduction of ICIs, at least 4 phase III trials of adjuvant immunotherapy after liver resection or radiofrequency ablation (RFA) are ongoing. Experimental arms are nivolumab, durvalumab/bevacizumab, pembrolizumab, and atezolizumab+bevacizumab (Table 1). The inclusion criteria for these trials are "a high risk of recurrence" patient subgroup. Macroscopic vascular invasion may have been regarded as "a very high risk of recurrence", and this patient condition was excluded in 3 studies. Only IMbrave 050, a study of atezolizumab+bevacizumab, accepted Vp1 or Vp2 patients.

Very recently, the IMbrave 050 study indicated a significantly better RFS for adjuvant atezolizumab +bevacizumab (*9*). This is the first phase III study showing the benefit of adjuvant therapy after liver resection or RFA. However, reaching a conclusion on survival benefits would be premature. IMbrave 050 is the only adjuvant study that included patients with limited vascular invasion, Vp1 and 2. However, they accounted

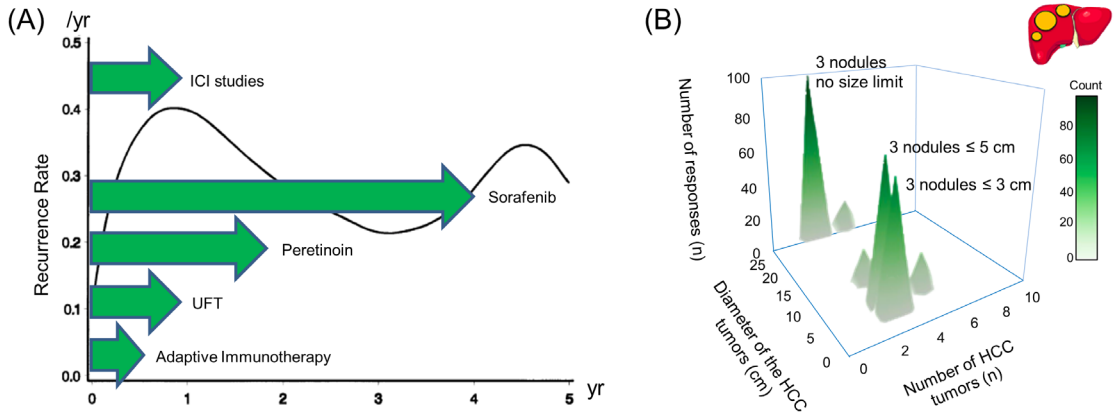

Figure 1. (A) Duration of adjuvant therapy superimposed on a risk of recurrence curve. (B) Upper limit of oncologically resectable (R) for multiple lesions in terms of the size and number of tumors. The x-axis shows the number of HCC tumors, the y-axis shows the maximum diameter of the HCC tumors (cm), and the z-axis shows the number of responses. Source: *Modified from Reference 2,15.*

Table 1. On-going phase III trials of adjuvant immunotherapy for HCC

Trial name	Drug	Target molecule	Duration of treatment	Primary endpoint	Target number of patients	Study start date
CheckMate 9DX	Nivolumab	PD1	1 yr	RFS	530	Dec. 2017
EMERALD-2	Durvalumab +/- Bevacizumab	PD-L1, VEGF	1 yr	RFS	888	Apr. 2019
KEYNOTE-937	Pembrolizumab	PD-L1	1 yr	RFS	950	May 2019
IMbrave 050	Atezolizumab + Bevacizumab	PD-L1, VEGF	1 yr	RFS	662	Dec. 2019

for only 6–8% of cases, and subgroup analysis was done only for cases with micro- instead of macro-vascular invasion. Further evaluation of the impact of ICIs after liver resection for HCC with macrovascular invasion may be needed.

After reviewing a long history of failures in adjuvant trials for HCC, there are several keys to success including appropriate patient selection, appropriate duration of adjuvant therapy, sufficient efficacy of the regimen, acceptable AEs, maintained performance status (PS), and liver function. Most of the ongoing trials might fulfill these conditions and their final results are awaited.

Neoadjuvant systemic therapy or conversion strategy

Another promising combination of surgery and systemic therapy is neoadjuvant therapy for potentially resectable cases or conversion strategy for oncologically unresectable cases. The conversion strategy for unresectable colorectal liver metastases (CRLM) was established more than a decade ago. After the introduction of FOLOX, FOLFIRI +/- mAbs, we could expect marked tumor shrinkage, making unresectable tumors into resectable ones. This strategy may not be simply applicable to HCC because the anti-tumoral action of systemic therapy on HCC differs slightly because dramatic tumor shrinkage is rare and a decrease in vascularity is more common.

Since lenvatinib was approved in 2018, there have been several reports on effective cases. For example, Matsuki *et al*. reported a case that initially involved a large tumor in the right liver and a lung metastasis. After lenvatinib administration, there was a marked shrinkage of the tumors and the metastatic lesion in the lung disappeared. This patient was ultimately able to undergo curative liver resection (*10*). The relatively high response rate (RR) to lenvatinib led us to plan a neoadjuvant trial for technically or oncologically unresectable HCCs (LENS-HCC trial: jRCT s031190057). There were 5 categories for patient inclusion. Category A is cases with macrovascular invasion, followed by category B, synchronous extrahepatic disease (EHD). Category C is a combination of A and B. Category D is cases with very large tumor loads where R0 resection is unlikely. The last category E is metachronous EHD. Forty-nine patients were recruited, and 33 patients (67%) were able to undergo liver resection and 16 were not. Although we may need a longer follow-up, the 24-month survival rate was over 75% in resected cases, which was much higher than that for unresectable cases (*11*).

A similar study is ongoing in Japan: the neoadjuvant atezolizumab plus bevacizumab RACB study, UMIN000046634). The inclusion criteria are the same as those for the lenvatinib trial. The target number of patients is 50, and it is expected to close soon (*12*). Recently, Kaseb *et al*. conducted a prospective study in a neoadjuvant setting to compare nivolumab and nivolumab plus ipilimumab: the blockade of the PD-1/PD-L1 and CTLA-4 pathways (*13*). Although efficacy was not a primary endpoint, CR was achieved in 29% of cases and there was no delay in surgery because of severe AEs. Patients with a major pathological response (MPR) has a significantly better RFS after liver resection.

Concept of borderline resectable HCC

In the field of pancreatic cancer, the concept of a borderline resectable tumor (BR) has been well established. Neoadjuvant therapy is usually used for BR pancreatic cancer according to National Center for Global Health and Medicine (NCGM) guidelines (14). Recently, the Japan Liver Cancer Association (JLCA) and the Japanese Society of HPB Surgery (JSHPBS) created a joint working group on "so-called borderline resectable HCC". First, they surveyed expert Japanese HBP surgeons to clarify their perceptions of the resectability of HCC. Then, an expert panel was organized to reach a consensus on oncological resectability for advanced HCC.

Akahoshi *et al*. analyzed a total of 351 responses from the aforementioned survey (*15*). Resectability for single tumors was broad in that 64.7% of the respondents considered solitary tumors to be R (resectable), irrespective of size. However, opinions diverged on the upper limit of the number of tumors/tumor size for R among multiple tumors: *i*) up to three nodules with no size limit (27.9%), *ii*) up to three nodules ≤ 5 cm in diameter each (21.4%), and *iii*) up to three nodules ≤ 3 cm in diameter each (19.4%, Figure 1B. Resectability for HCC with portal vein invasion depended on the extent of vascular invasion: Vp1, Vp2, Vp3, and Vp4 were considered to be R by 90.9%, 70.7%, 39.0%, and 8.0% of respondents, respectively. Half of the respondents indicated they would consider resection even for cases with extrahepatic spread under limited conditions.

Based on the aforementioned survey data, the expert panel (*i.e.*, joint working group) reached a Japanese consensus on "so-called borderline resectable HCC" that has been published on the websites of JLCA and JSHPBS. Here are the definitions for R: resectable, BR1, and BR2. Surgery may offer better survival outcomes for the R category compared to other treatments. Surgical intervention as a part of multi-disciplinary treatment may offer survival benefits for the BR1 category. The effectiveness of surgery is indeterminate and surgical indications should be carefully determined under the standard multidisciplinary management for the BR2 category. We decided not to use the term "UR or unresectable" for the BR2 category because "UR" may be misleading since most of the cases are technically resectable and the patient's surgical option may be limited from the beginning due to the label UR.

In conclusion, recent dramatic progress in systemic therapy has harkened the advent of an era

of a combination strategy for HCC. Several adjuvant ICI regimens are being studied, and IMbrave 050 demonstrated a promising clinical benefit. Neoadjuvant or perioperative systemic therapy for advanced HCC is another clinical question that warrants further investigation. The definition of resectability or borderline resectability provides a common language regarding advanced HCC for investigators and is a useful tool for future clinical trials.

Funding: None.

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

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Received January 9, 2024; Accepted January 29, 2024.

Released online in J-STAGE as advance publication February 6, 2024.

**Address correspondence to*:
Norihiro Kokudo, National Center for Global Health and Medicine, 1-21-1 Toyama Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: nkokudo@hosp.ncgm.go.jp

Global Health & Medicine. 2024; 6(3):174-182.
ORIGINAL ARTICLE
DOI: 10.35772/ghm.2023.01108

Prevalence and associated factors of low vigor in patients living with HIV and hemophilia in Japan: A cross-sectional observational study

Kensuke Komatsu[1,2,*], Sota Kimura[1], Yoko Kiryu[1], Aki Watanabe[3], Ei Kinai[4], Shinichi Oka[1], Satoshi Kimura[5], Junko Fujitani[6], Mikiko Ogata[1], Ryogo Minamimoto[7], Masatoshi Hotta[7], Kota Yokoyama[7,8], Tomoyuki Noguchi[9], Koubun Imai[10]

[1] AIDS Clinical Center, National Center for Global Health and Medicine, Tokyo, Japan;
[2] Faculty of Human Sciences, Wako University, Tokyo, Japan;
[3] Tokyo Metropolitan Children's Medical Center, Tokyo, Japan;
[4] Department of Laboratory Medicine, Tokyo Medical University Hospital, Tokyo, Japan;
[5] The Center for Education and Research of Infection Prevention and Control, Tokyo Healthcare University, Tokyo, Japan;
[6] Department of Rehabilitation, National Center for Global Health and Medicine, Tokyo, Japan;
[7] Department of Radiology, National Center for Global Health and Medicine, Tokyo, Japan;
[8] Department of Radiology, Tokyo Medical and Dental University, Tokyo, Japan;
[9] Department of Radiology, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan;
[10] Department of Psychiatry, Hitachi Medical Education and Research Center, University of Tsukuba Hospital, Ibaraki, Japan.

Abstract: People living with human immunodeficiency virus (HIV) are at high risk of mental health problems. However, little is known about this risk in HIV-infected patients with hemophilia (HPH) who contracted the virus through blood products. This cross-sectional, observational study assessed patients' mood states and the factors associated with them among Japanese HPH to evaluate the need for psychosocial support. HPH completed self-administered questionnaires (Profile of Mood States [POMS] and General Health Questionnaire-28), neuropsychological tests, and brain magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography/computerized tomography scans. HIV-infected patients with no hemophilia (HPnH) completed POMS and neuropsychological tests. Socio-demographic characteristics and HIV- and hemophilia-related data were obtained from participants' medical records and interviews. A Mann–Whitney *U* test and chi-squared analyses were conducted. Fifty-six HPH and 388 HPnH completed the questionnaires and neuropsychological tests. HPH had a significantly lower prevalence of tension–anxiety (HPH, 7%; HPnH, 18%; $p = 0.049$) and a significantly higher prevalence of low vigor (HPH, 63%; HPnH, 32%; $p < 0.001$). Low vigor in HPH was significantly associated with impaired executive function (low vigor, 66%; high vigor, 33%; $p = 0.019$) and a social dysfunction score ≥ 3 (moderate; low vigor, 26%; high vigor, 5%; $p = 0.047$). Our results highlight the high prevalence of low vigor among HPH, leading to impairments in executive and social functions. Therefore, healthcare workers need to pay attention to the vigor, executive function, and social function of HPH.

***Keywords*:** mental health, blood products, mood states, executive function, psychosocial support, healthcare

Introduction

People living with human immunodeficiency virus (HIV) are at high risk of mental illness or mental health problems (*1*). Mental health and mental illness are not the same. Mental health includes emotional, psychological, and social well-being. It affects how we think, feel, and act. It also helps determine how we handle stress, relate to others, and make healthy choices. Mental illness collectively refers to all diagnosable mental disorders, such as depression, anxiety, bipolar disorder, or schizophrenia (*2*). Mental health is a concept that encompasses mental illness and includes mental and psychological conditions that are not diagnosed as illnesses. Poor mental health or mental illness can contribute to poorer healthcare behaviors across the HIV care continuum, leading to negative HIV health outcomes (*i.e.*, elevated viral load (VL), decreased CD4+ levels, and increased opportunistic illnesses) (*3,4*). Depression can increase the risk of mortality among people living

with HIV (*5,6*). The World Health Organization recommends that attention to the mental health of people living with HIV should be an integral part of HIV care and that an integrated approach to HIV, mental health, and psychosocial problems is needed (*7*).

However, most previous studies on the mental health and mental illness of people living with HIV target patients for whom the virus was sexually transmitted, with few studies targeting HIV-infected patients with hemophilia (HPH) who were infected through blood products (*8-12*). In the 1970s and 1980s, many patients with hemophilia worldwide became infected with HIV through contaminated products. For example, nearly 5,000 (*i.e.,* half of all patients), 1,300, and 1,200 patients with hemophilia were infected in the United States of America, the United Kingdom, and France, respectively (*13-15*). In addition, recent reports indicate that approximately 50–80% of those infected with HIV have already died (*15,16*). In Japan, 1,432 patients with hemophilia became infected with HIV through contaminated products in the mid-1980s (*17*). As of 2023, 697 HPH are still alive and entering their fifties (*17,18*). As HPH are a minority group of people living with HIV, their mental health and potential mental illnesses have not been adequately considered. Catalan *et al.* found that HIV-seropositive men with hemophilia had higher levels of psychological distress and sexual problems than HIV-seronegative men with hemophilia (*12*). However, Marsettin *et al.* reported that HIV-seropositive and -seronegative men with hemophilia presented the same degree of emotional involvement; there were no significant differences in the average scores between groups – either on the anxiety or depression scales (*8,11*). In addition, Drotar *et al.* (*9*) found that HIV-seropositive children and adolescents with hemophilia demonstrated psychological resilience and levels of psychological adjustment comparable to their seronegative counterparts. While many studies on mental health problems of HPH were in the pre-anti-retroviral therapy (ART) era, there is no unified view on this subject in the post-ART era.

A meta-analysis of mental health disorders in patients with hemophilia suggested that the prevalence of depression, anxiety, and attention-deficit/hyperactivity disorder across decades is significantly higher in patients with hemophilia compared to the general population (*19*). HPH are exposed to stigma and discrimination about HIV as well as comorbidities such as hemophilic arthropathy, muscle hemorrhage, and hepatitis C virus (HCV) infection (*20*). Therefore, even if they do not have a mental illness, their mental health may be poorer than that of non-HPH. Thus, it is important to investigate the mental health associated with HPH in the post-ART era.

We used the Profile of Mood States (POMS) (*21,22*) and General Health Questionnaire (GHQ)-28 (*23,24*) to investigate mental health problems among HPH. The POMS scale assesses temporal mood states that change according to condition and allows simultaneous assessment of six subscales: tension–anxiety, depression–dejection, anger–hostility, vigor, fatigue, and confusion. Assessing a variety of moods is important for this study because moods influence our overall sense of well-being and impact behavior patterns and perceived health (*25*). The GHQ-28 is a screening device for identifying minor psychiatric disorders (somatic symptoms, anxiety and sleeplessness, social dysfunction, and depression) (*23,24*). This study assessed mental health problems of Japanese HPH in the post-ART era using the POMS and GHQ-28 and examined the associated factors to evaluate the need for psychosocial support.

Participants and Methods

Participants and procedures

Participants were HPH who received outpatient treatment from May 2016 to February 2018 at the National Center for Global Health and Medicine (NCGM) in Tokyo, Japan. Exclusion criteria were determined based on the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders 5th ed. (DSM-5) (*12*). The exclusion criteria were as follows: *i*) individuals currently with an active AIDS-defining illness requiring treatment; *ii*) those with congenital mental retardation; *iii*) those diagnosed with major depressive disorder and/or schizophrenia; *iv*) individuals diagnosed with Alzheimer's disease, frontotemporal lobar degeneration, Lewy body dementia, prion diseases, Parkinson's disease, and/or Huntington's disease; *v*) those with cerebrovascular disease; *vi)* those with traumatic brain lesion; *vii*) individuals who were habitual illicit drug users and/or severe alcoholics; *viii*) those undergoing treatment for central nervous system opportunistic disease or with clear physical impediments; *ix*) those exhibiting other pathologies that clearly caused cognitive impairment; *x*) those with a fever ≥ 38.5°C or any active infectious symptoms during examination; *xi*) individuals for whom neuropsychological (NP) testing was judged to be performed inaccurately; and *xii*) those who had undergone NP testing within the past year. Patients with acute or subacute lesions detected on brain magnetic resonance imaging (MRI) that could potentially impact cognitive function, as well as patients with foreign materials that were deemed unsuitable for an MRI scan, were also excluded (*12*).

When applicable patients visited the hospital for an outpatient visit, the coordinator provided a written explanation of this study and obtained written consent. Thereafter, patient information was collected from medical records. Other necessary information was collected by interviews on the morning of the POMS, GHQ, and NP testing day. Psychiatric diagnosis was based on a brief screening using the Mini International Neuropsychiatric Interview (*26*). In addition, a single

psychiatrist, a board-certified doctor of psychiatry with more than 20 years of clinical psychiatric experience, examined all HPH.

Data for the control group comprising HIV-infected patients with no hemophilia (HPnH) were obtained from NCGM from the J-HAND study (for more details, see Kinai *et al.* (*27*)). Three time zones (9 a.m. to 10 a.m., 10 a.m. to 11 a.m., and 11 a.m. and later) were set at each of three outpatient examination rooms. Patients who met the selection criteria were recruited in the order of visit time, and verbal consent was obtained from up to three patients per day in each room. The control group included 388 randomly extracted Japanese HIV-infected patients who received outpatient treatment at the NCGM between July 2014 and July 2016 (route of infection: sexual transmission, n = 385; other and unknown, n = 3). Participant exclusion criteria were in accordance with DSM-5 (*12*).

Measures

Socio-demographic characteristics and HIV- and hemophilia-related factors

The following data were obtained from the medical records and interviews: age, sex, education level, current employment, presence of partner or housemate, history of smoking, current alcohol use and amount, documented HIV transmission route, history of AIDS-defining illness, and incomplete virologic suppression, defined as two or more times of HIV-RNA ≥ 200 copies/mL – after virologic suppression or after 24 weeks on ART, current treatment for hypertension, diabetes and hyperlipidemia, HCV coinfection, qualitative Treponema pallidum latex agglutination (TPHA), time since HIV diagnosis, nadir CD4 cell count, current CD4 cell count, highest VL, current VL, ART regimen, time on ART, Hemophilia A or B, history of cerebrovascular disorder, and presence of hemophilic arthropathy. Body temperature and systolic and diastolic blood pressures were measured on the same day. Using blood samples obtained within three months of NP tests, we measured hemoglobin, serum triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, and hemoglobin A1c levels.

POMS

Mood was assessed using the Japanese edition of the POMS (*21,22*). The POMS is a 30-item self-report questionnaire used to assess psychological distress. It measures mood using six subscales: tension–anxiety, depression–dejection, anger–hostility, vigor, fatigue, and confusion. The POMS total mood disturbance score is calculated by summing the scores across all six factors, while weighing vigor negatively. Respondents were asked to rate the degree to which an adjective was applied to them during the preceding week on a five-point scale (0 = "not at all" and 4 = "extremely"). Scores for each subscale ranged from 0 to 20, with higher scores indicating more severe symptoms, except for the vigor scale, in which lower scores indicated more severe symptoms (*28*). The Cronbach's alpha was 0.760 in this study and showed acceptable internal consistency.

GHQ

Mental states were assessed using the 28-item Japanese version of the GHQ (*23,24*). The GHQ assesses general psychopathology and measures mental state using four scales: somatic symptoms, anxiety/insomnia, social dysfunction, and severe depression; these were summed to obtain a total score. Respondents were asked to rate each item according to the degree to which it was applicable during the preceding two or three weeks. Two scoring systems were used: a Likert scale and a two-point scale. On the Likert scale, the four possible answers, "better than usual", "same as usual", "worse than usual", and "much worse than usual", were assigned scores of 0, 0, 1, and 1, respectively. The minimum possible total score for each scale was 0, and the maximum possible score was 7. The Cronbach's alpha was 0.756 in this study and showed acceptable internal consistency.

NP tests

Participants' NP states were assessed using the 14 NP tests for eight cognitive domains: Verbal Fluency (category and letter) in verbal/language (*29*), Digit Span (forward and backward) in attention/working memory (*30*), Trail Making Test (TMT)-A (*31*) and Digit Symbol Subset (*30*) in speed of information processing, TMT-B (*31*) in executive function, Rey-Osterrieth Complex Figure test (ROCFT) (*32,33*) in visuospatial construction, ROCFT (immediate) and Story Memory Test (SMT) (*34*) in verbal and visual learning, ROCFT (delayed recall), SMT (delayed recall), and Grooved Pegboard (dominant and non-dominant) (*35*) in motor skills.

Assessment of imaging

Brain MRIs were performed on a clinical 3.0-Tesla MRI unit (MAGNETOM Verio; Siemens AG, Erlangen, Germany). These included three-dimensional T1-weighted images (magnetization-prepared 180° radio-frequency pulses and rapid gradient-echo sampling) used for the computed analysis of Voxel-based Specific Regional Analysis System for Alzheimer's disease (*36*), T2-weighted images to evaluate microbleeding, MR angiography to evaluate cerebrovascular disorder, diffusion-weighted images to evaluate acute or subacute cerebrovascular attack, and T2-weighted images and fluid-attenuated inversion recovery images to evaluate general brain disorders. All MRIs were evaluated by an observer (TN) with 10 years of experience in neuroradiology.

For brain fluorodeoxyglucose positron emission tomography/computerized tomography (FDG-PET/

CT), ^{18}F-FDG was synthesized in the hospital using a cyclotron (F200, Sumitomo Heavy Industries, Ltd.) at the NCGM. Participants fasted for > 6 h. After resting for more than 15 min with an eye mask in a decubitus position in a dark, quiet room, the ^{18}F-FDG (5 MBq/kg; lower limit, 185 MBq; upper limit, 370 MBq) was injected intravenously. The conditions described were maintained until imaging was performed. Imaging was initiated with PET/CT equipment (Biograph mCT S20; Siemens Medical Solutions) 45 min after ^{18}F-FDG administration. Blood glucose levels at the time of scanning were confirmed to be ≤ 200 mg/dL in all participants. The PET data were analyzed using the data analysis software SIEMENS, MI Neurology, in which 18 regions were set: left/right frontal lobes, left/right temporal lobes, left/right parietal lobes, left/right cingulate and paracingulate gyri, left/right central regions, left/right occipital lobes, left/right basal ganglia, left/right mesial temporal lobes, and left/right cerebellum. The ^{18}F-FDG accumulation in each region (mean standardized uptake value; SUV) was measured, and the standard deviations (SD) of the mean SUV were compared. The mean value of the accumulation in the left and right regions, of which the SD was the smallest, was set as the value for the control region. The ratios of the values of the other 16 regions to the control value (SUVr) were calculated for the assessment.

Statistical analysis

A chi-squared analysis was used to compare the prevalence of mood problems between HPH and HPnH. Mood problems included *t*-scores of 60 and above on the five subscales of the POMS: tension–anxiety, depression–dejection, anger–hostility, and fatigue and confusion (*22*). The *t*-scores for mild to moderate problems ranged from 60 to 75, and those for severe problems ranged from 76 and above for *t*-score in five subscales. On the vigor scale, low vigor was a mood problem and included a *t*-score of 40 and below. Mild to moderate problems ranged from 26 to 40, and severe problems were 25 and below for the *t*-score in vigor. Data were expressed as the median (interquartile range [IQR]). To investigate the factors associated with low vigor in HPH, a Mann–Whitney *U* test and chi-squared analyses with two groups (high and low vigor in HPH) were conducted. Serious issues regarding health were indicated by a score of 5 or more points for the total GHQ score. Moreover, in the GHQ subscale, moderate symptoms were indicated by a score of 4 or higher in somatic symptoms, and 3 or higher in anxiety/insomnia, social dysfunction, and severe depression (*23,24*). In addition, regarding the assessment of imaging, the Mann–Whitney *U* test was performed to compare the two groups (high and low vigor in HPH). Tests were two-tailed, with $\alpha = 0.05$ as the criterion for significance. All data were analyzed using IBM SPSS Statistics 26.0. Values of $p < 0.05$ were considered statistically significant.

Ethical considerations

This cross-sectional observational study was approved by the ethics committee of the National Center for Global Health and Medicine (NCGM; Nos. NCGM-G-001973-0 and NCGM-G-003055-00). This study followed the principles of the Declaration of Helsinki. All study participants provided written informed consent prior to study enrollment.

Results

Eighty-two HPH received outpatient treatment at the NCGM. Of these, eight patients satisfied exclusion criteria, nine patients refused to participate in this study, one patient withdrew consent for participation, and one patient did not undergo the POMS, GHQ, or NP testing during the study period; thus, 63 patients underwent the testing and medical examination by a psychiatrist. Ten patients were diagnosed with psychiatric disorders: schizophrenia ($n = 1$), bipolar disorder ($n = 1$), dysthymia ($n = 2$), developmental disorder ($n = 2$), alcoholism ($n = 1$), and sleep disorder ($n = 3$). Of these, three patients with psychiatric disorders that could affect cognitive function (schizophrenia, bipolar disorder, and alcoholism) and four patients with unavailable recent brain imaging findings were excluded. Finally, 56 patients were included in the analysis.

Regarding the control group comprising HPnH, 716 HIV-infected patients were recruited; 205 patients were excluded based on the exclusion criteria, and the remaining 388 patients completed the same tests, except for GHQ-28, brain MRI, and FDG-PET/CT scans. The routes of HIV infection in HPnH included sexual transmission ($n = 385$) and other and unknown ($n = 3$). In Japan, the transmission route is relatively identifiable; thus, when a patient is diagnosed with HIV infection, the doctor is required to confirm the symptoms and transmission route with the patient and notify the health center. This information was used in this study.

Mood problems in HPH and HPnH

Figure 1 shows the differences in the prevalence of mood problems between HPH and HPnH. HPH had a significantly lower prevalence of tension–anxiety (HPH, 7%; HPnH, 18%; $p = 0.049$, power = 0.445) and a significantly higher prevalence of low vigor (HPH, 63%; HPnH, 32%; $p < 0.001$, power = 0.859).

Association factors with low vigor in HPH

Table 1 shows the sample characteristics and factors associated with low vigor among HPH. Regarding the factors associated with low vigor in HPH, socio-

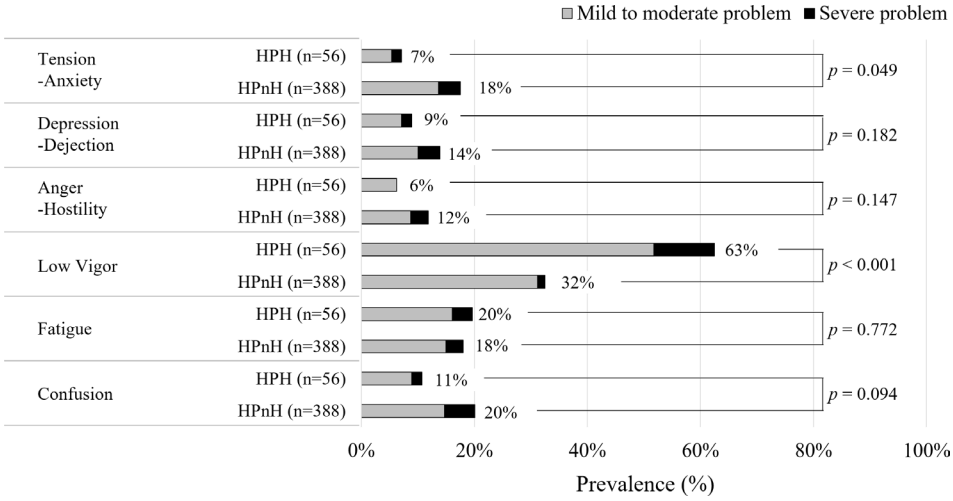

Figure 1. Prevalence of mood problems among HIV-infected patients with hemophilia (HPH) and HIV-infected patients with no hemophilia (HPnH).

demographic factors – neither HIV-related nor hemophilia-related factors – were significantly associated with vigor. However, compared with high vigor, low vigor was significantly associated with impaired executive function (low vigor, 66%; high vigor, 33%; $p = 0.019$, power = 0.4) and a social dysfunction score ≥ 3 (low vigor, 26%; high vigor, 5%; $p = 0.047$, power = 0.438). In addition, there was no difference in FDG accumulation between the high- and low-vigor groups (Table 2).

Discussion

This is one of the few studies to analyze the mental health problems of HPH in the post-ART era. Previous studies have reported low psychosocial distress and psychological quality of life in hemophilia patients in the post-ART era (*37,38*). Hirabayashi *et al.* (*37*) reported that psychological quality of life scores in patients with hemophilia were lower than those in patients with sexually transmitted infections in Japan. Further, Talaulikar *et al.* (*38*) reported that patients with chronic coagulation disorders had significantly lower vitality, general health, and physical role limitation in the measurement of health-related quality of life, compared with normative data obtained from the Australian Bureau of Statistics. Imai *et al.* (*12*) reported that HPH had a higher rate of neurocognitive dysfunction than HPnH, particularly impaired executive function.

One of the most important findings of this study is that the prevalence of low vigor among HPH was 63%, which is much higher than that among HPnH, even though they did not have a mental illness. This study suggests that low vigor among HPH is associated with a higher rate of impaired executive function and social dysfunction compared with high vigor.

Various factors can influence vigor. The reasons for low vigor among HPH were as follows: organic changes in the brain, poor exercise habits, and psychological distress owing to HIV-related stigma or multimorbidity. Long-term exposure of the central nervous system to HIV leads to organic changes in the brain. HPH were infected with HIV in the 1980s and, therefore, have likely been infected with HIV for longer than HPnH (*12*). However, the results indicate that the influence of organic factors in the brain on vigor could be less, as there was no difference in FDG accumulation between the high- and low-vigor groups.

Low vigor among HPH could be associated with exercise habits. Patients with hemophilia could have poorer exercise habits than those without hemophilia, as they have been restricted from an early age to prevent bleeding. Physical exercise enhances executive function and improves positive moods, such as vigor (*39-42*). Healthcare workers' assessment of their physical capabilities, along with the degree of hemophilic arthropathy and the risk of bleeding, can enhance their vigor. In addition, proposing an exercise program tailored to each HPH could lead to further improvement. However, to clarify these associations, multivariate analyses on HPH with vigor, executive function, and social function, using exercise habits as an indicator, as well as comparative studies involving HPH and HPnH, should be conducted. It could also be useful to conduct intervention studies to create moderate exercise programs tailored to the physical function of HPH and examine the effects of such programs on vigor, executive function, and social function.

The HPH group also experienced psychological distress owing to HIV-related stigma or multimorbidity for many years (*20,43*). Some studies have suggested an association between HIV-related stigma and psychological distress or mood (*44,45*). Long-term experiences of HIV-related stigma could have prevented HPH from connecting with people and society, affected various life events such as employment and marriage,

Table 1. Participant characteristics and association factors with low vigor in HIV-infected patients with hemophilia

Characteristics	Total *n* = 56	High Vigor (T-score > 40) *n* = 21	Low Vigor (T-score ≤ 40) *n* = 35	*p*-value
Socio-demographic characteristics				
Age (years), median (IQR)	47 (43–54)	45 (43–54)	48 (42–55)	0.728
Older than 50 years, *n* (%)	24 (43)	8 (38)	16 (46)	0.577
Gender (Male), *n* (%)	56 (100)	21 (100)	35 (100)	-
Educational level (university or higher), *n* (%)	21 (38)	8 (38)	13 (37)	0.943
Employed, *n* (%)	36 (64)	15 (71)	21 (60)	0.388
Living alone, *n* (%)	14 (25)	3 (14)	11 (31)	0.151
Current or recent smoking, *n* (%)	30 (54)	13 (62)	17 (49)	0.333
Alcohol use, *n* (%)	19 (34)	9 (43)	10 (29)	0.274
History of illicit drug use within 12 months, *n* (%)	0 (0)	21 (100)	35 (100)	-
Hypertension (SBP ≥ 140 or DBP ≥ 90 mmHg), *n* (%)	24 (43)	11 (52)	13 (37)	0.265
Diabetes (HbA1c ≥ 7.0 or on treatment), *n* (%)	9 (16)	3 (14)	6 (17)	0.778
Anemia (Male <12 g/dL, Female <10 g/dL), *n* (%)	9 (16)	2 (10)	7 (20)	0.301
HCV-Ab positive, *n* (%)	55 (98)	21 (100)	34 (97)	0.434
TPHA positive, *n* (%)	0 (0)	21 (100)	35 (100)	-
HIV-related factors				
Time since diagnosis (month), median (IQR)	314 (273–332)	408 (404–411)	408 (404–414)	0.799
History of AIDS-defining illness, *n* (%)	7 (13)	3 (14)	4 (11)	0.754
Current CD4 (cells/mm^3), median (IQR)	525 (342–662)	520 (336–631)	540 (342–765))	0.283
Nadir CD4 (cells/mm^3), median (IQR)	141 (91–184)	150 (70–167)	131 (87–199)	0.788
Current HIV-RNA < 20 (copies/mL), *n* (%)	49 (89)	18 (86)	31 (91)	0.528
History of incomplete virological suppression, *n* (%)	20 (36)	8 (38)	12 (34)	0.773
Current antiretroviral therapy use, *n* (%)	55 (98)	20 (95)	35 (100)	0.375
Current antiretroviral treatment				
NNRTI-based regimen, *n* (%)	15 (27)	4 (19)	11 (31)	0.311
PI-based regimen, *n* (%)	18 (32)	5 (24)	13 (37)	0.301
INSTI-based regimen, *n* (%)	41 (73)	16 (76)	25 (71)	0.697
Hemophilia-related factors				
Hemophilia A, *n* (%)	45 (80)	17 (81)	28 (80)	0.609
Hemophilia B, *n* (%)	11 (20)	4 (19)	7 (20)	
Presence of history of cerebrovascular disorder, *n* (%)	13 (23)	2 (10)	11 (31)	0.056
Presence of hemophilic arthropathy, *n* (%)	30 (54)	9 (43)	21 (60)	0.213
Neuropsychological factors				
Neuropsychological impairment, *n* (%)	27 (48)	9 (43)	18 (51)	0.534
Impaired cognitive domain				
Verbal/language, *n* (%)	2 (4)	1 (5)	1 (3)	0.614
Attention/working memory, *n* (%)	7 (13)	1 (5)	6 (17)	0.176
Speed of information processing, *n* (%)	13 (23)	3 (14)	10 (29)	0.186
Executive function, *n* (%)	30 (54)	7 (33)	23 (66)	0.019
Visuospatial construction, *n* (%)	14 (25)	5 (24)	9 (26)	0.873
Verbal and visual learning, *n* (%)	10 (18)	4 (19)	6 (17)	0.857
Verbal and visual memory, *n* (%)	8 (14)	3 (14)	5 (14)	0.644
Motor skills, *n* (%)	9 (16)	1 (5)	8 (23)	0.075
GHQ-28				
Somatic symptoms score ≥ 4 (moderate), *n* (%)	14 (25)	3 (14)	11 (31)	0.151
Anxiety/insomnia score ≥ 4 (moderate), *n* (%)	8 (14)	3 (14)	5 (14)	0.644
Social dysfunction score ≥ 3 (moderate), *n* (%)	10 (18)	1 (5)	9 (26)	0.047
Severe depression score ≥ 3 (moderate), *n* (%)	4 (7)	0 (0)	35 (11)	0.143

HCV-Ab, hepatitis C antibody; TPHA, Treponema pallidum latex agglutination; NRTI, Nucleoside reverse transcriptase inhibitor; NNRTI, Non-nucleoside reverse transcriptase inhibitor; PI, Protease inhibitor; INSTI, integrase inhibitors; GHQ, General Health Questionnaire.

and reduced their vigor. Multimorbidity – the presence of two or more chronic physical conditions (*46*) – may also influence the vigor of HPH. Patients with multimorbidity tend to experience psychological distress (*47*). HPH have many chronic physical conditions, such as hemophilic arthropathy, muscle hemorrhage,

Table 2. Comparison of SUVr values between high and low vigor in HIV-infected patients with hemophilia (HPH)

	Total $n = 55$	High Vigor (T-score > 40) $n = 21$	Low Vigor (T-score ≤ 40) $n = 34$	*p*-value
Frontal lobe (L)	1.17 (1.10–1.23)	1.17 (1.11–1.26)	1.17 (1.10–1.22)	0.499
Frontal lobe (R)	1.18 (1.09–1.23)	1.18 (1.10–1.26)	1.18 (1.09–1.23)	0.579
Temporal lobe (L)	1.15 (1.08–1.21)	1.16 (1.09–1.19)	1.14 (1.08–1.21)	0.377
Temporal lobe (R)	1.19 (1.10–1.24)	1.19 (1.11–1.23)	1.18 (1.10–1.26)	0.795
Parietal lobe (L)	1.15 (1.09–1.23)	1.18 (1.12–1.24)	1.12 (1.09–1.24)	0.368
Parietal lobe (R)	1.17 (1.10–1.24)	1.18 (1.11–1.22)	1.17 (1.10–1.25)	0.903
Cingulate and paracingulate gyri (L)	1.17 (1.12–1.24)	1.17 (1.14–1.25)	1.17 (1.09–1.24)	0.556
Cingulate and paracingulate gyri (R)	1.21 (1.15–1.28)	1.21 (1.16–1.29)	1.22 (1.14–1.27)	0.621
Central region (L)	1.12 (1.05–1.17)	1.12 (1.05–1.16)	1.12 (1.06–1.17)	0.678
Central region (R)	1.14 (1.06–1.20)	1.14 (1.08–1.20)	1.14 (1.06–1.20)	0.568
Occipital lobe (L)	1.16 (1.12–1.23)	1.18 (1.12–1.23)	1.16 (1.11–1.23)	0.591
Occipital lobe (R)	1.21 (1.14–1.26)	1.22 (1.15–1.28)	1.21 (1.13–1.25)	0.640
Basal ganglia (L)	1.22 (1.15–1.27)	1.20 (1.16–1.27)	1.23 (1.14–1.27)	0.959
Basal ganglia (R)	1.18 (1.15–1.23)	1.17 (1.14–1.23)	1.18 (1.14–1.23)	0.652
Mesial temporal lobe (L)	0.91 (0.87–0.96)	0.91 (0.87–0.96)	0.91 (0.87–0.95)	0.903
Mesial temporal lobe (R)	0.92 (0.88–0.97)	0.92 (0.88–0.98)	0.92 (0.88–0.96)	0.795
Thalamus (L)	1.16 (1.11–1.25)	1.22 (1.11–1.26)	1.15 (1.11–1.24)	0.416
Thalamus (R)	1.17 (1.09–1.23)	1.20 (1.09–1.24)	1.14 (1.09–1.23)	0.579

Data are median (interquartile range; IQR). SUVr, Standard uptake value ratio; L, left; R, right.

HCV, hemophilia, and HIV infection; therefore, their vigor could have been low. Although the association between a history of cerebrovascular disorder and low vigor was not significant in this study, a significant trend was observed. It is quite difficult to remove HIV-related stigma from society or to cure multimorbidity completely. However, providing a space (*e.g.*, mental health counseling, psychotherapy, or self-help groups) where these patients can feel comfortable talking about the long-term emotional burden of these problems could help prevent a decline in vigor or mental health deterioration. In addition, previous studies suggest that supplementation with a multi-vitamin/mineral leads to improved vigor ratings and improved cognitive performance (*48-50*). Therefore, we suggest that healthcare workers pay attention to the vigor, executive function, and social function of HPH – even if they do not have a mental illness – and that they help HPH enhance their health through exercise tailored to the physical condition of each patient, by offering mental healthcare, or by promoting the use of multi-vitamin-mineral supplements.

Despite its valuable findings, our study had some limitations. First, although the facility from which participants were recruited is one of the largest hospitals in Japan providing HIV treatment and treating several HPH, our sample was not representative of the entire population of HPH in Japan. Second, the sample size of 56 HPH was insufficient to conduct statistical testing and compare the high- and low-vigor groups; therefore, a multicenter survey should be conducted to increase the sample size and improve the accuracy of the results in the future. Third, two or more psychiatrists should be asked to examine a patient's mental status to further improve the accuracy of psychiatric diagnosis. Fourth, although this study applied a self-administered anonymous questionnaire – the POMS and GHQ-28 – potentially biased self-reports cannot be ruled out.

In conclusion, the prevalence of low vigor among Japanese HPH without mental illness is high. Those with low vigor had impairments in executive and social functions. Therefore, healthcare providers should approach patients' low vigor by suggesting exercise programs that are appropriate for their physical and medical condition, providing a safe space to talk about the problems of living with multimorbidity in a society with HIV-related stigma, and promoting the use of multi-vitamin supplements. Thereafter, the effectiveness of such interventions should be scientifically tested.

Acknowledgements

The authors express their gratitude to the members of the AIDS Clinical Center, National Center for Global Health and Medicine: Hiroyuki Gatanaga, Yoshimi Kikuchi, Katsuji Teruya, Junko Tanuma, Kunihisa Tsukada, Koji Watanabe, Takahiro Aoki, Daisuke Mizushima, Yasuaki Yanagawa, Haruka Uemura, Naokatsu Ando, Daisuke Shiojiri, Hirohisa Yazaki, Ikumi Genka, Kiyoto Tsuchiya, Kazuko Ikeda, Miwa Ogane, Yuko Sugino, Beni Taniguchi, Hitomi Suzuki, Asami Kurita, Naomi Abe, Hukuko Osugi, Akane Soldano, Yoshimi Abe, and Ken Otomo.

Funding: This study was supported by Grant-in-Aid for AIDS research from the Japanese Ministry of Health, Labour and Welfare to S.K. (no. H27-AIDS-Shitei-002), S.O. (no. H28-AIDS-Ippan-002) and J.F. (no. 22HB2004), and a grant from the NCGM to E.K. (no. 26-G-102).

Conflict of Interest: Ei Kinai received research grants from Chugai Pharmaceutical and CSL Behring and honoraria from Gilead Sciences, ViiV Healthcare, MSD, Chugai Pharmaceutical, Sanofi, Bayer, Takeda Pharmaceutical, Novo Nordisk, Fujimoto Pharmaceutical Corporation, and CSL Behring. Shinichi Oka received research grants from ViiV Healthcare and Gilead Sciences and honoraria from Gilead Sciences and ViiV Healthcare. The remaining authors have no conflicts of interest to disclose.

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Received October 20, 2023; Revised April 14, 2024; Accepted April 30, 2024.

Released online in J-STAGE as advance publication May 4, 2024.

Address correspondence to:
Kensuke Komatsu, AIDS Clinical Center, National Center for Global Health and Medicine, 1-21-1 Toyama Shinjuku-ku, Tokyo 162-8655, Japan; Faculty of Human Sciences, Wako University, 5-1-1 Kanaigaoka, Machida-shi, Tokyo 195-8585, Japan.
E-mail: k.komatsu@wako.ac.jp

Global Health & Medicine. 2024; 6(3):183-189.
ORIGINAL ARTICLE
DOI: 10.35772/ghm.2023.01085

Gallbladder fossa nodularity in the liver as observed in alcoholic liver disease patients: Analysis based on hepatobiliary phase signal intensity on gadoxetate-enhanced MRI and extracellular volume fraction calculated from routine CT data

Keisuke Sato[1,§], Shinji Tanaka[1,§], Hiroshi Urakawa[2], Ryo Murayama[1], Eiko Hisatomi[1], Yukihisa Takayama[1], Kengo Yoshimitsu[1,*]

[1] Department of Radiology, Faculty of Medicine, Fukuoka University, Fukuoka, Japan;
[2] Department of Radiology, Fukuoka University Chikushi Hospital, Chikushino, Japan.

Abstract: The purpose of this study is to further verify the concept utilizing signal intensity on hepatobiliary phase (HBP) of gadoxetate-enhanced MRI and extracellular volume fraction (ECV) calculated from CT data. Between Jan 2013 and September 2018, consecutive ALD patients who had both quadruple phase CT and gadoxetate-enhanced MRI within six months were retrospectively recruited. Those who had any intervention or disease involvement around gallbladder fossa were excluded. All images were reviewed and ECV was measured by two experienced radiologists. GBFN grades, and their HBP signal intensity or ECV relative to the surrounding background liver (BGL) were analyzed. There were 48 patients who met the inclusion criteria. There were GBFN grade 0/1/2/3 in 11/15/18/4 patients, respectively. The signal intensity on HBP relative to BGL were iso/slightly high/high in 30/15/3 patients, respectively, and ECV ratio (ECV of GBFN divided by that of BGL) was 0.88 ± 0.18, indicating there are more functioning hepatocytes and less fibrosis in GBFN than in BGL. The GBFN grades were significantly correlated to relative signal intensity at HBP (Spearman's rank correlation, $p < 0.01$, rho value 0.53), and ECV ratio ($p < 0.01$, rho value -0.45). Our results suggest GBFN in ALD would represent liver tissues with preserved liver function with less fibrosis, as compared to BGL, which are considered to support our hypothesis as shown above.

***Keywords*:** gallbladder fossa, nodularity, alcoholic liver disease, gadoxetate uptake, extracellular volume fraction

Introduction

Recently, it has been reported that nodularity of the gallbladder fossa (GBFN) as observed typically in patients with alcoholic liver disease (ALD) may represent spared area from portal venous perfusion containing alcohol absorbed in the gastrointestinal tract, escaped from alcohol-induced fibrotic and atrophic change of the surrounding background liver (BGL) parenchyma, due to cholecystic venous drainage (CVD) (*1-5*). Pathologically, it has been shown GBFN consists of unusually large-sized pseudo-lobules in contrast to small-sized pseudo-lobules that are known to be characteristic of alcoholic liver cirrhosis, which may as well be called "pseudo-hyperplasia" (*1,6*).

As a morphological feature of ALD-related cirrhosis as compared to those due to other etiologies, the enlargement of segment I or caudate lobe is well known (*7,8*). GBFN may serve as an adjunctive sign for ALD, with relatively high specificity but with low sensitivity, as compared to caudate lobe enlargement (*1*).

We hypothesized that, if GBFN represents relatively hyperplastic liver tissue in contrast to fibrotic BGL, gadoxetate uptake, which is a marker of functioning hepatocytes (*9-11*), at GBFN should be preserved, as compared to the surrounding fibrotic BGL, at the hepatobiliary phase (HBP) of gadoxetate-enhanced MRI (EOB-MRI). Further, we also hypothesized that the extracellular volume fraction (ECV), which has been reported to be a useful surrogate biomarker for pathological degree of liver fibrosis (*12-16*), of GBFN, should be low as compared to that of BGL. The purpose of this study is to further clarify the etiology or mechanism of GBFN, using its HBP signal intensity on EOB-MRI and ECV calculated from CT data relative to those of BGL as analytic indices.

Materials and Methods

Patients

Between January 2013 and September 2018, consecutive ALD patients who underwent both quadruple phase dynamic CT and EOB-MRI within six months in our institute were retrospectively recruited. Among those, patients who had had cholecystectomy and hepatectomy, apparent acute cholecystitis or cholangitis, hepatocellular carcinoma (HCC) involving gallbladder fossa, and tumor thrombus involving the 1st order branch or main trunk of the portal vein were excluded. Those who had any interventions around GBF, such as transarterial (chemo) embolization, radiofrequency ablation, or microwave ablation, between the two examinations, were also excluded.

Clinical diagnosis of ALD was made for patients with liver dysfunction without serological evidence of hepatitis B or C infection, or anti-mitochondrial or anti-nuclear antibodies, and with history of habitual alcohol overconsumption, based on the criteria defined by Japanese Society of Biomedical Research of Alcohol (*17*), that is, briefly, 60g /day and 40g/day or more alcohol consumption for men and women, respectively. Institutional review board approved this study and waived obtaining informed consent from the patients because of its retrospective nature (U20-02-008). Also of note is that the study was conducted in compliance with the Declaration of Helsinki.

MR protocol

MR equipment used was a 3T Discovery 750W (GE, Milwaukee, USA), and HBP images were obtained with fat saturated 3D gradient-echoT1 weighted sequences under breath-holding and that with diaphragmatic navigation, 15 min after the intravenous injection of gadoxetate (Primovist®, Bayer Health Care, Osaka, Japan). Details of the MRI protocol are shown in Supplemental Table S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=78*).

CT protocol

Two CT instruments were used in this study. One was an area-detector CT (Aquilion ONE ViSION Edition, Canon Medical Systems, Tokyo, Japan), and scanning parameters were as follows: 0.5 mm × 80 row, 120 kVp, three-dimensional auto-exposure control (Volume EC: SD12@5 mm), 0.5 sec/rotation, 0.813 beam pitch, 512 × 512 matrix, 300–350 mm field-of-view, and 2 mm reconstruction. Noise reduction was achieved using a hybrid iterative reconstruction (ADIR 3D Weak). The other CT used was 64-row multi-detector CT (Aquilion 64, Canon Medical Systems, Tokyo, Japan), with parameters shown below: 0.5 mm × 64 row, 120 kVp, three-dimensional auto-exposure control (Volume EC: SD12@5 mm), 0.5 sec/rotation, 0.828 beam pitch, 512 × 512 matrix, 300–350 mm field-of-view, and 2mm reconstruction (filtered back projection). Portal venous phase was additionally reconstructed along the coronal plane with 2 mm contiguous slice thickness in either CT.

After obtaining unenhanced images, 600 mg/kg iodine contrast medium (Iopamiron 370, Bayer Health Care, Osaka, Japan) was injected for 30 sec at a variable injection rate, and arterial dominant phase images were obtained using a bolus tracking method, followed by portal dominant phase at 60 sec, and equilibrium phase images at 240 sec after the commencement of contrast medium injection.

ECV map generation

ECV map was generated from pre-contrast and equilibrium phase CT data, according to the previously reported method (*14-16*). Just briefly, because ECV is defined as (100- hematocrit) * Δ liver /Δ blood pool, where Δ represents the difference in the CT values between the unenhanced and equilibrium phase (*12-16*), ECV map was generated on the dedicated workstation by means of subtracting unenhanced images from equilibrium phase images utilizing a non-linear non-rigid anatomical correction algorithm, and inputting the hematocrit value for each patient (*14-16*).

Assessment

All qualitative assessments were performed by two radiologists (KS and ST) independently first, and disagreement was resolved by consensus. The grades of GBFN were assessed, separately for CT and MRI, according to the definitions as previously reported (*1*): just briefly, grade 0 represents flat surface of the gallbladder fossa (GBF) without notch or protrusion; grade 1, minimal protrusion with slight notch at GBF; grade 2, slight protrusion with notches, the degree of which is between grade 1 and grade 3; grade 3, apparent nodularity of GBF. After determining GBFN grades, the two radiologists independently assessed HBP signal intensity of GBFN relative to BGL both on axial and coronal images, and higher signal on either plane was adopted to represent the patient. The quantitative assessment, namely, ECV measurement, was performed by the same two radiologists (KS and ST) independently for the first 20 patients to assess inter-observer agreement. One radiologist (KS) performed ECV measurement for the rest of the patients. ECV was measured by placing as large an oval-shaped region-of-interest (ROI) as possible on ECV map as generated from pre-contrast and equilibrium phase CT data, as previously reported (*14-16*). As for GBFN EVC measurement, ROI was placed in its center. As for ECV

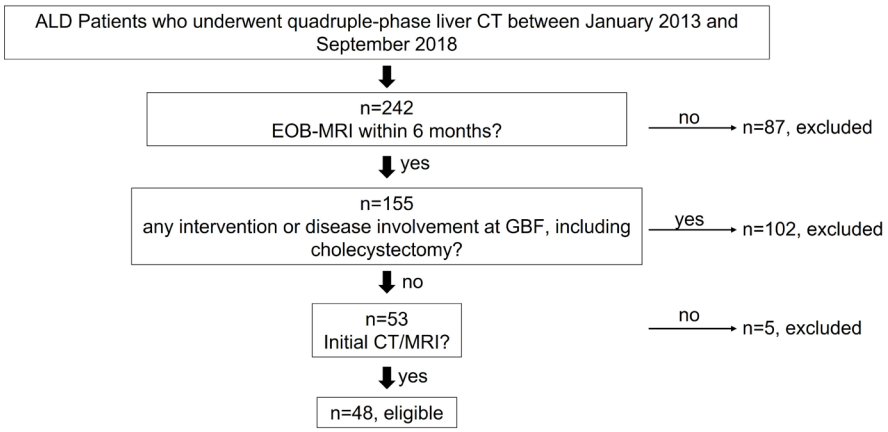

Figure 1. Patient inclusion flow chart. ALD: alcoholic liver disease, EOB-MRI: gadoxetate-enhanced MRI, GBF: gallbladder fossa.

measurement for BGL, ROIs were placed in the anterior, posterior, and medial segments, because these three segments were considered to be anatomically closely related to gallbladder fossa; and their averaged value was used to represent ECV of BGL. For the anterior and medial segment measurement, the axial slice slightly cephalad to GBFN was selected where both middle hepatic vein and the anterior branch of portal vein were clearly visualized. For posterior segment measurement, the same slice as GBFN visualized was selected, and ROIs were carefully placed avoiding apparent vessels, masses or artifacts. The ECV of GBFN divided by that of BGL was defined as ECV ratio. The grades of HBP signal intensity and ECV ratio were correlated to modified albumin-bilirubin (mALBI) grades (*18,19*), which is an indicator of liver function in CLD patients. Blood sample data were selected from the date, which was closest to that of CT for mALBI assessment and ECV calculation.

Statistics

Inter-observer concordance for qualitative assessment was assessed with kappa statistics, and that for quantitative assessment, namely, ECV, was evaluated by intra-class coefficient (ICC). Univariable analysis was performed with *t*-test, Fisher's exact probability test, or Tukey-Kramer's HSD test for parametric variables, and with Mann-Whitney test, or Wilcoxon's rank test, for non-parametric variables. Correlation for non-parametric variables was assessed using Spearman's rank correlation test. *P* values less than 0.05 were considered statistically significant. All statistical analyses were performed using JMP Pro13.0.0 (SAS corporation, Cary, USA).

Results

Patients

Patient selection flow chart is shown in Figure 1. There were 48 patients for whom both CT and MRI were obtained within six months, without history of any intervention around the gallbladder fossa. Among these, 5 patients had two sets of CT and MRI, for whom the initial set was adopted for this study. There were 43 men and 5 women, with an average age of 60.6 years. Of the 48 patients, 41 were included in the previous study (*1*). Details of the demographic data of the patients are shown in Table 1. The interval between CT and blood sampling was 3.2 ± 4.3 days (range 0–20).

Table 1. Demographic data and GBFN information of 48 ALD patients

Characteristic	Values
Age	60.6 ± 10.9 (range 28-83)
Sex	M:F = 43:5
mALBI grade	1/ 2a/ 2b/ 3 = 14/ 9/ 2/ 3
CP grade/score	A5/ A6/ B7/ B8/ B9 /C10 = 20/ 14/ 5/ 4/ 4/ 1
GBFN grade	0/ 1/ 2/ 3 = 11/ 15/ 8/ 4
HBP signal intensity	Iso/ slightly high/ high = 30/ 15/ 3
ECV of GBFN	31.5 ± 7.7 (range 14.6 – 50.4)
ECV of BGL	36.4 ± 7.8 (range 22.6 – 53.2)
ECV ratio	0.88 ± 0.18 (range 0.53 – 1.36)

ALD: alcoholic liver disease, M/F: male/female, mALBI: modified albumin-bilirubin, CP: Child-Pugh, GBFN: gallbladder fossa nodularity, HBP: hepatobiliary phase, ECV: extracellular volume fraction, BGL: background liver, P/N: positive/negative.

GBFN and related factors assessment

Kappa value for the two radiologists in assessing the grades of GBFN was 0.68, showing good agreement. That for signal intensity of GBFN on HBP was 0.85, showing excellent agreement. Final GBFN grades were identical for CT and MRI.

There was a weak, but significantly positive correlation between GBFN grades and mALBI grades (Spearman's rank correlation, $p < 0.05$, rho value 0.34), namely, the higher the grades of GBFN, the higher mALBI grade is (more severely impaired liver function) (Table 2). HBP signal intensities of GBFN

Table 2. Correlation between GBFN grades and modified ALBI grades

Items	mALBI				Total
	Grade 1	Grade 2a	Grade 2b	Grade 3	
GBFN					
Grade 0	8	0	3	0	11
Grade 1	4	3	7	1	15
Grade 2	1	4	11	2	18
Grade 3	1	2	1	0	4
Total	14	9	22	3	48

There was a significantly positive correlation between GBFN grades and ALBI grades (Spearman's rank correlation, $p < 0.05$, rho value 0.34). GBFN: gallbladder fossa nodularity, mALBI: modified Albumin-Bilirubin grade.

Table 3. Correlation between GBFN grades and HBP signal intensity relative to surrounding BGL on gadoxetate-enhanced MRI

Items	HBP signal intensity relative to BGL			Total
	Iso	slightly high	high	
GBFN				
Grade 0	11	0	0	11
Grade 1	12	3	0	15
Grade 2	6	10	2	18
Grade 3	1	2	1	4
Total	30	15	3	48

There was a moderately positive correlation between GBFN grades and HBP signal intensity relative to BGL (Spearman's rank correlation, $p = 0.003$, rho value 0.53). GBFN: gallbladder fossa nodularity, HBP: hepatobiliary phase, BGL: background liver.

relative to BGL were iso, slightly high, and high, in 30, 15, and 3 patients, respectively. There was a moderate and significantly positive correlation between grades of GBFN and HBP signal intensity relative to BGL (Spearman's rank correlation, $p < 0.001$, rho value 0.53), namely, the higher the GBFN grade, the higher HBP signal intensity relative to BGL (Table 3).

As for ECV measurement, ECV of GBFN was 31.7 ± 10.1 for observer 1, and 29.8 ± 13.3 for observer 2, showing ICC of 0.87, whereas ECV of BGL (average of three segments) was 36.6 ± 10.3 for observer 1, and 38.0 ± 14.1 for observer 2, with an ICC of 0.75, both showing good agreement, for the first 20 patients. ECV ratio was 0.88 ± 0.18 for all 48 patients, suggesting there is less fibrotic tissue in GBFN as compared to BGL. Paired *t*-test also showed there is a significant difference between ECV of GBFN and that of BGL ($p < 0.0001$). There was a strong, significantly negative correlation between GBFN grades and ECV ratio (Spearman's rank correlation, $p < 0.01$, rho value -0.45), namely, the higher the GBFN grade, the lower the ECV ratio (Figure 2).

Lastly, we additionally assessed the correlation between ECV ratio and HBP signal intensity, which showed significant correlation (Figure 3, Spearman's rank correlation, $p < 0.01$, rho value -0.42).

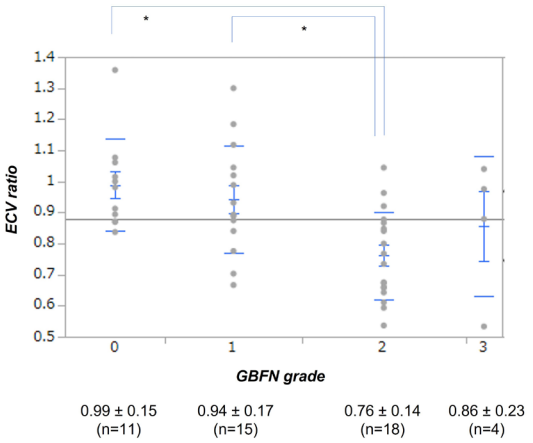

Figure 2. Correlation between gallbladder fossa nodularity (GBFN) grades and extracellular volume fraction (ECV) ratio. There was a statistically significant difference (*) in ECV ratio between GBFN grades 0 and 2 (Tukey-Kramer's HSD test, $p = 0.0032$), and between grades 1 and 2 ($p = 0.013$). Spearman's rank correlation suggested significantly negative correlation between GBFN grades and ECV ratio ($p = 0.0013$, rho value -0.452).

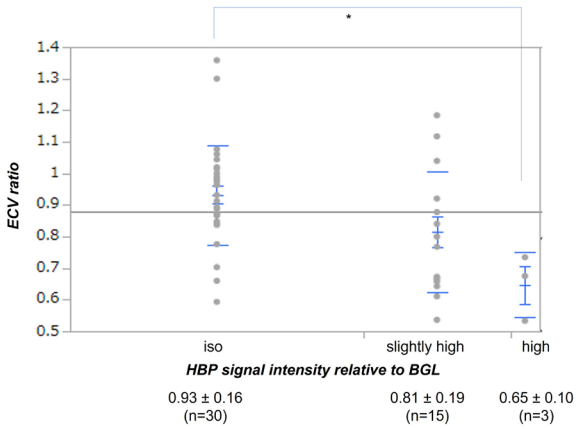

Figure 3. Correlation between extracellular volume fraction (ECV) ratio and hepatobiliary phase (HBP) signal intensity relative to surrounding background liver (BGL) on gadoxetate-enhanced MRI. There was a statistically significant difference (*) in ECV ratio between iso-intensity and high intensity (Tukey-Kramer's HSD test, $p = 0.019$). Spearman's rank correlation suggested significantly negative correlation between ECV ratio and HBP signal intensity ($p = 0.0027$, rho value -0.424).

Representative cases are shown in Figures 4–6, all of whom show similar to higher signal intensity of GBFN as compared to background liver, and ECV ratio of around 0.6.

Discussion

In this study, we tried to further verify our hypothesis that GBFN typically observed in ALD patients may represent "pseudo-hyperplastic" liver parenchyma around GBF, escaping from alcohol containing portal perfusion due to cholecystic venous drainage (*1,6*), from viewpoints

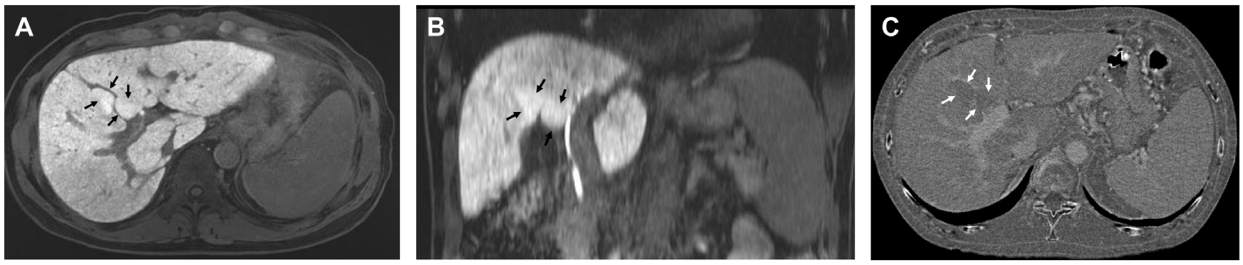

Figure 4. A 47-year-old man with alcoholic liver disease (ALD). Child-Pugh grade/score was A/6, and modified albumin-bilirubin grade/score was 2a/-2.5. An apparent nodularity (arrows) is observed at the gallbladder fossa (GBF) around the neck. GBF nodularity grade 3 was assigned. **(A)** Hepatobiliary phase axial image of gadoxetate-enhanced MRI. GBFN exhibits slightly higher signal intensity (arrows) than the surrounding background liver. **(B)** Oblique coronal reconstruction image of hepatobiliary phase of gadoxeate-enhanced MRI. GBFN exhibits slightly higher signal intensity than the surrounding background liver (arrows). **(C)** Extracellular volume fraction (ECV) map calculated from CT obtained 3 months before MRI through the slice corresponding to 4**A**. ECV of GBFN (arrows) was 20%, whereas that of background liver ECV (average of anterior, posterior, and medial segments, not shown) was 30%. ECV ratio was 0.67. Note GBFN of apparent low ECV value (arrows).

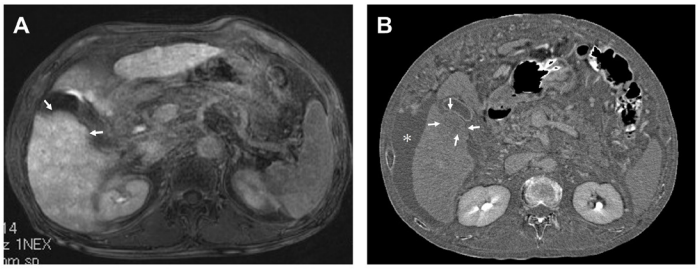

Figure 5. A 61-year-old man with alcoholic liver disease (ALD). Child-Pugh grade/score was A/5, and modified albumin-bilirubin grade/score was 1/-3.0. A slight nodularity (arrows) is appreciable at the gallbladder fossa (GBF). GBF nodularity grade 2 was assigned. **(A)** Hepatobiliary phase image of gadoxetate-enhanced MRI. GBFN exhibits almost similar signal intensity as the surrounding background liver (arrows). **(B)** Extracellular volume fraction (ECV) map calculated from CT obtained 4 months after MRI. There is apparent increase in the volume of ascites (*) as compared to 5**A**. ECV of GBFN was 26%, whereas that of background liver (average of anterior, posterior, and medial segments, not shown) was 45%. ECV ratio was 0.59. Note GBFN of apparent low ECV value (arrows).

Figure 6. A 60-year-old woman with alcoholic liver disease. Child-Pugh grade/score was A/5, and modified albumin-bilirubin grade/score was 2/-2.0. A faint nodularity (arrows) is appreciable at the gallbladder fossa (GBF). GBF nodularity grade 1 was assigned. **(A)** Hepatobiliary phase image of gadoxetate-enhanced MRI. GBFN exhibits higher signal intensity than the surrounding background liver. **(B)** Extracellular volume fraction (ECV) map calculated from CT obtained 3 months before MRI. ECV of GBFN was 27%, whereas that of background liver (average of anterior, posterior, and medial segments, not shown) was 44%. ECV ratio was 0.61. Note GBFN of apparent low ECV value (arrows). **(C)** Unenhanced CT for anatomical correlation of GBFN with 6**B**.

of HBP signal intensity on EOB-MR and ECV obtained from routine CT data.

Gadoxetate is a hepatocyte-specific contrast agent, taken up *via* organic anion-transporting polypeptide (OATP) as expressed on the cellular membrane of hepatocytes, and it has been known that in patients with liver dysfunction or liver cirrhosis, parenchymal enhancement decreases, typically at the HBP images of EOB-MRI, along with decreased expression of OATP (*11*). Our results that HBP signal intensity of GBFN was similar to (two thirds) or higher (one third) than that of BGL, and also that its grade was positively correlated to GBFN grades, would support the above-mentioned hypothesis.

ECV of the liver has drawn attention as a biomarker of pathological grades of liver fibrosis (*12-16*). ECV is

a sum of intravascular and extravascular extracellular spaces, which can be easily calculated from non-contrast and equilibrium phase CT data of routine clinical practice, because the concentration of iodine is considered the same for both intravascular and extravascular spaces at the equilibrium phase (*12-16*). We have reported the usefulness of ECV map, which is generated by subtracting precontrast images from equilibrium phase images utilizing a non-linear non-rigid anatomical correction algorithm specifically adjusted to upper abdominal organs (*14-16*), and promising results have been obtained for the estimation of degree of liver fibrosis (*14*). Thanks to the highly accurate subtraction algorithm, the anatomical misregistration is minimized in this ECV map, and therefore precise ECV can be obtained for any small area of any part of the liver (*16*), like GBFN. Our results that ECV of GBFN is significantly less than that of BGL, along with overall ECV ratio being less than 1 (0.88), and GBFN grades negatively correlated to ECV ratio, would also support the above-mentioned hypothesis.

Our results suggested GBFN is characterized by relatively higher signal intensity on HBP and less ECV as compared to the surrounding BGL, indicating that areas of GBFN is closer to normal liver tissue as compared to the BGL affected by alcohol. This knowledge would help radiologists understand the morpho-radiological features of the liver in CLD patients, particularly those with ALD.

There are several limitations of this study. Due to its retrospective nature, there could be a bias in patient selection. That this is a single arm study dealing with only ALD patients without any control cohort to compare, could be another limitation. Because the previous study (*1*) showed GBFN of mild grades (up to grade 2) can be observed in chronic hepatitis C patients as well, although less frequently than in ALD patients, we focused on an ALD patient cohort in this study to make it easier to clarify the characteristic features in HBP signal intensity and ECV values. It is possible that GBFN in patients with CLD of other etiologies may show different tendencies, which should be clarified in future studies. Lack of pathological proof in any of our study population is another limitation, however, it would be ethically difficult to justify obtaining histological specimens of GBFN in ALD patients. Furthermore, as mentioned earlier, there is a recent pathological investigation (*6*) confirming the presence of GBFN as a pseudo-hyperplastic change in autopsy ALD cases, which would be sufficient as a pathological support for our hypothesis. Finally, the subjective way of assessing the grades of GBFN and HBP signal intensity, or manual ECV measurement, may be included as a limitation, however, the kappa values or ICC in our study suggested agreements between the two radiologists were reasonably high.

In conclusion, GBFN tends to show higher HBP signal intensity on EOB-MRI and lower ECV calculated from CT data as compared to the surrounding BGL, which is considered to support the hypothesis that GBFN is "pseudo-hyperplastic" liver parenchyma around gallbladder fossa, escaping from alcohol-containing portal venous perfusion due to CVD.

Acknowledgements

Authors greatly thank Professor Fumihito Hirai, Department of Gastroenterology, Faculty of Medicine, Fukuoka University, and also Professor Suguru Hasegawa, Department of Gastroenterological Surgery, for providing patients' clinical information.

Funding: None.

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

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Received August 6, 2023; Revised December 25, 2023; Accepted January 29, 2024.

Released online in J-STAGE as advance publication March 15, 2024.

[§]*These authors contributed equally to this work.*
**Address correspondence to*:
Kengo Yoshimitsu, Department of Radiology, Faculty of Medicine, Fukuoka University, 7-45-1 Nanakuma Jonan-ku, Fukuoka City 814-0180, Japan.
E-mail: kengo@fukuoka-u.ac.jp

Global Health & Medicine. 2024; 6(3):190-198.
ORIGINAL ARTICLE
DOI: 10.35772/ghm.2023.01113

Low preoperative hemoglobin A1c level is a predictor of perioperative infectious complications after esophagectomy: A retrospective, single-center study

Daiki Kato[1,2], Kazuhiko Yamada[1,2,*], Naoki Enomoto[1], Syusuke Yagi[1], Hanako Koda[1], Kyoko Nohara[1]

[1] Department of Surgery, National Center for Global Health and Medicine, Tokyo, Japan;
[2] Course of advanced and Specialized Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan.

Abstract: This retrospective, single-center study aimed to evaluate the impact of blood glucose (BG) markers on perioperative complications after esophagectomy in a cohort of 176 patients. Study analyses included the correlation of daily maximum BG level and hemoglobin A1c (HbA1c) with clinicopathological factors. Maximum BG levels were significantly higher on postoperative day (POD) 0 than on PODs 2, 3, 5, and 7 ($p < 0.05$). Additionally, maximum BG levels on PODs 1, 2, and 7 were significantly higher in patients with preoperative HbA1c levels of ≥ 5.6% than in those with preoperative HbA1c levels of < 5.6% ($p < 0.05$ for all). The rates of any complications and infectious complications were higher in patients with preoperative HbA1c levels of < 5.6% than in those with preoperative HbA1c levels of ≥ 5.6% ($p < 0.05$ for both). A preoperative HbA1c level of < 5.6% was a significant predictor of infectious complications after esophagectomy by logistic regression analysis ($p < 0.05$). Maximum BG level after esophagectomy remained high in patients with high preoperative HbA1c levels, whereas a normal HbA1c level was an independent risk factor for infectious complications.

***Keywords*:** blood glucose, esophageal surgery, postoperative hyperglycemia, HbA1c

Introduction

Despite considerable advances in surgical techniques, esophageal surgery remains associated with high morbidity and mortality (*1-3*). Many patients undergoing esophagectomy experience postoperative hyperglycemia due to increased stress and intraoperative administration of steroids to prevent postoperative acute respiratory distress syndrome. Studies investigating the relationship between blood glucose (BG) and infectious complications after esophageal surgery revealed the association of high BG levels on postoperative days (PODs) 3–5 with infectious complications, including pneumonia. Studies also reported that a high BG level was a predictor of morbidity and mortality (*4-7*).

Hemoglobin A1c (HbA1c) is a useful marker to evaluate long-term BG control over the previous 8–12 weeks in patients with diabetes, with its significant impact on perioperative mortality and prognosis demonstrated in many surgical procedures (*8,9*). Intriguingly, lower HbA1c levels were reported to be associated with worse prognosis after esophagectomy (*10*). In management of patients admitted to the intensive care unit (ICU), lower or higher HbA1c levels can significantly impact morbidity and mortality (*11*).

In the present study, we investigated changes in maximum BG (mBG) levels after esophagectomy and the impact of daily mBG and preoperative HbA1c levels on perioperative complications. Our analyses revealed that mBG levels remained high in patients with high preoperative HbA1c levels and that a high mBG level was not associated with perioperative complications. However, a normal preoperative HbA1c level was an independent risk factor for infectious complications in patients undergoing esophagectomy.

Patients and Methods

Patients

This was a retrospective study including 233 consecutive patients who underwent esophagectomy for esophageal cancer from January 2013 to October 2021 in the Department of Surgery, National Center for Global Health and Medicine. Among these, 55 patients, including 24, 5, 9, 14, and 3 patients who underwent two-stage surgery, esophageal bypass surgery, proximal gastrectomy of junctional cancer, salvage surgery after definitive chemoradiation, and exploratory thoracotomy, respectively, were excluded. Additionally, one patient

with missing data on preoperative HbA1c was excluded. Therefore, the final analysis included 176 patients (Figure 1). The study was conducted after approval by the National Center for Global Health and Medicine Review Board (NCGM-G-004166-00).

Perioperative glucose control

All patients received methylprednisolone at 250 mg/body weight before esophagectomy to prevent postoperative acute respiratory distress syndrome. After surgery, all patients were admitted to the ICU, and postoperative BG levels were monitored every 6 h, starting at the time of ICU admission, and continuous insulin therapy using an insulin pump was performed in patients with BG levels of >150 mg/dL. The continuous insulin dose was adjusted to maintain BG levels below 150 mg/dL. In patients with BG levels of ≤ 100 mg/dL, the dose of continuous insulin was reduced. In patients with hypoglycemia (BG level < 70 mg/dL), insulin was discontinued and 20 mL of 20% glucose was administered until the BG level reached ≥ 80 mg/dL.

Perioperative nutrition therapy

In all patients, we inserted central venous catheter or peripherally inserted central venous catheter before surgery and we underwent catheter jejunostomy or gastrostomy from stomach roll during esophagectomy. Postoperative nutritional therapy was performed through continuous intravenous or enteral feeding. For daily caloric intake, the central venous catheter was used and enteral caloric intake from jejunostomy was gradually increased to provide 80–100% of the required calories until POD 7. Jejunal tube feeding was initiated with a protein-enriched digestive nutrients at 200 kcal/day on POD 1, and the amount was increased to 400 and 800 kcal/day on PODs 3 and 5, respectively. Starting on POD 7, the diet was changed to semidigested nutrients at 1,200 kcal/day. Subsequent nutritional therapy was adjusted as appropriate depending on the oral intake status of each patient.

Study design

The present study was designed to investigate changes in mBG levels until POD 7 and to explore the relationship of mBG and preoperative HbA1c levels with perioperative complications. In addition, risk factors for infections complications and the relationship of HbA1c level with nutritional markers and prognosis were analyzed. mBG level was defined as the highest daily BG level on PODs 0, 1, 2, 3, 5, and 7. Hypoglycemia was defined as a BG level below 70 mg/dL. HbA1c was measured before surgery in an outpatient setting. The cutoff value for the HbA1c level with the best predictive accuracy was determined using receiver operating characteristic curve analysis. Postoperative complications were defined using the Common Terminology Criteria for Adverse Events version 5.0, and complications related to surgical procedures were evaluated according to the Clavien–Dindo classification (*12*).

Statistical analysis

All statistical analyses were performed using JMP version 17 software (SAS Institute, Cary, NC). We investigated the relationship of preoperative HbA1c and postoperative mBG levels with various clinical factors. The clinical factors included age, sex, body mass index, Eastern Cooperative Oncology Group performance scale score, history of smoking, comorbidities, American Society of Anesthesiologists (ASA)-physical status (PS) score, Charlson comorbidity index (*13*), albumin, prealbumin, hemoglobin, prognostic nutritional index, controlling nutrition status score, tumor location, TNM stage, histology, operation time, blood loss, approach (thoracic *vs*. abdominal), lymphadenectomy, and postoperative complications. Data were presented as medians with interquartile ranges. The Mann–Whitey *U*

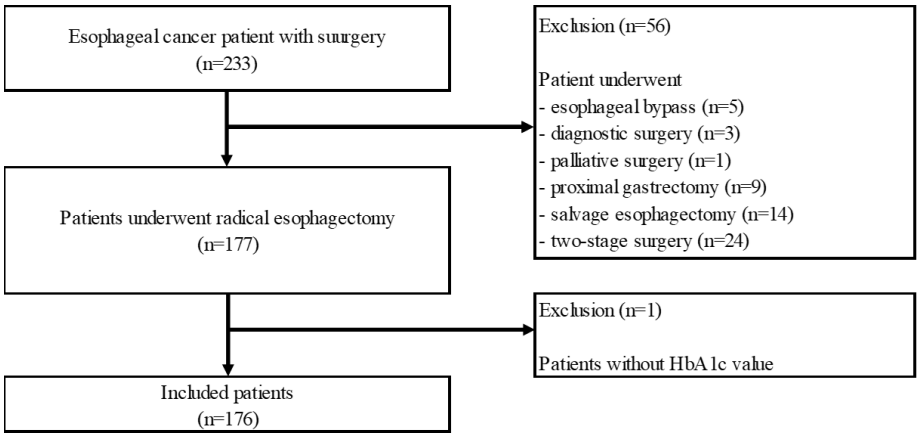

Figure 1. Inclusion criteria.

test was used for comparisons between two groups; the chi-square or Fisher's exact test was used to compare qualitative variables; and the Kruskal–Wallis test was used to compare quantitative variables. Univariate analysis was performed to identify risk factors for infectious complications, and variables were selected using backward elimination for multivariate logistic regression analysis. In all statistical analyses, a p value of < 0.05 indicated statistical significance.

Results

Patients

Table 1 summarized the characteristics of patients included in the study. The median age was 70 (62–76) years, and 143 (81%) patients were male. Preoperative diabetes was present in 28 (16%) patients, with a median preoperative HbA1c level of 5.9% (5.6–6.2%), and 151 (86%) patients had a preoperative Charlson comorbidity index score of >3. The cohort included 63 (41%), 24 (14%), 49 (28%), and 40 (22%) patients with clinical stage I, II, III, and IV esophageal cancer, respectively. Neoadjuvant chemotherapy or chemoradiotherapy was administered in 98 (56%) patients. Thoracoscopic and laparoscopic surgical approaches were employed in 135 (77%) and 100 (57%) patients, respectively. Three-field lymph node dissection was performed in 121 (69%) patients. The operation time and blood loss were 610 (545–667) min and 180 (86–351) mL, respectively. Clavien–Dindo grade II or higher complications within 30 days after surgery were noted in 114 (65%) patients, and infectious complications occurred in 79 (45%) patients. Pneumonia and anastomotic leakage occurred in

Table 1. Patient characteristics

Variables	n = 176
Age (years)	
Median (IQR)	70 (62-76)
Sex	
Male/Female (%)	143/33 (81%/19%)
BMI	
Median (IQR)	21.6 (19.9-23.5)
PS (ECOG)	
0/1/2/3 (%)	102/44/27/3 (58%/25%/15%/2%)
History of smoking	
yes / no (%)	145/31 (18%/82%)
Comobidities	
Diabetes mellitus	
yes / no (%)	28/148 (16%/84%)
Hypertension	
yes / no (%)	71/105 (40%/60%)
Pulmonary disease	
yes / no (%)	23/153 (13%/87%)
PS (ASA)	
1/2/3/4 (%)	6/119/51/0 (3%/68%/29%/0%)
CCI	
0-2/3-5/6 or above	25/101/50 (14%/57%/29%)
Laboratory findings	
HbA1c (%)	
Median (IQR)	5.9 (5.6-6.2)
Albumin (mg/dL)	
Median (IQR)	3.9 (3.5-4.2)
Prealbumin (mg/dL)	
Median (IQR)	24.6 (21-30)
Hemoglobin (g/dL)	
Median (IQR)	12.2 (10.7-13.5)
PNI	
Median (IQR)	45.5 (41.6-49.6)
CONUT	
0-1/2-4/5-8/9 or above	74/67/18/1 (46%/42%/11%/1%)
Tumor Locations	
Ce/Ut/Mt/Lt/Jz	8/37/60/54/14 (4%/21%/34%/31%/10%)

Table 1. Patient characteristics (continued)

Variables	n = 176
TNM (UICC 8th)	
cT	
1/2/3/4 (%)	62/14/68/32 (35%/8%/38%/19%)
cN	
0/1/2/3 (%)	72/67/32/5 (41%/38%/18%/3%)
cM	
0/1 (%)	163/13 (93%/7%)
cStage	
I/II/III/IV (%)	63/24/49/40 (36%/14%/28%/22%)
Histology	
SCC/Adenocarcinoma/other	153/18/5 (87%/10%/3%)
Preoperative treatment	
None/chemotherapy/CRT (%)	78/79/19 (44%/45%/11%)
Operation time (min)	
Median (IQR)	610 (545-667)
Blood loss (mL)	
Median (IQR)	180 (86-351)
Thoracic approach	
Open/VATS (%)	41/135 (77%/23%)
Abdominal approach	
Open/HALS/Laparoscopy (%)	76/12/88 (43%/50%/7%)
Lymphadectomy	
2 field/3 field (%)	55/121 (31%/69%)
Postoperative complications	
Clavien-Dindo classification	
Grade 0, 1/2 or higher (%)	62/114 (35%/65%)
Infectious complication	
yes / no (%)	79/97 (45%/55%)
Pneumonia	
yes / no (%)	47/129 (27%/73%)
Anastomotic Leakage	
yes / no (%)	25/151 (14%/86%)
Others	
yes / no (%)	26/150 (85%/15%)

IQR interquartile range, *BMI* body mass index, *PS* performance status, *ECOG* Eastern Coopelative Oncology Group, *ASA* American Society of Anesthesiologists physical status, *CCI* Charlson comobidity index, *HbA1c* hemoglobin A1c, *PNI* prognostic nutritional index, *CONUT* controlling nutritional status, *Ce* cervical esophagaus, *Ut* upper third of thoracic esophagus, *Mt* middle third of thoracic esophagus, *Lt* lower third of thoracic esophagus, *Jz* abdominal esophagus, *UICC* Union for International Cancer Control, *SCC* squamous cell carcinoma, *VATS* video assisted thoracic surgery, *HALS* hand assisted laparoscopic surgery

47 (27%) and 25 (14%) patients, respectively.

Changes in mBG and HbA1c levels

Table 2 and Figure 2 show the changes in mBG levels between PODs 0 and 7 after esophagectomy. The median mBG level was highest on POD 0 (205 [182–234] mg/dL), with gradual decreases observed on POD 1 and 2 (185 [162–216] and 151 [137–169] mg/dL, respectively). The mBG levels correlated with other variables (Figure 2). On the other hand, hypoglycemia (< 70 mg/dL) occurred in 19 (11%) patients. Additionally, the median mBG levels on POD 1, 2, and 7 were significantly higher in patients with a preoperative HbA1c level of ≥ 5.6% (*n* = 133) than in those with a preoperative HbA1c level of < 5.6% (n = 43) (Table 3).

Postoperative complications associated with mBG and HbA1c levels

Table 4 shows the mBG levels on POD 0–7 in patients with perioperative complications. On POD3, the mBG levels were higher in patients with any complication (p = 0.014), in those with infectious complications (p = 0.009), and in those with pneumonia (p < 0.001) compared to those without these complications. Similar differences were not observed in other PODs. On the other hand, the rates of infectious complications and pneumonia were higher in those with high mBG levels (≥180 mg/dL) than in those with low mBG levels (<180 mg/dL) (37% *vs*. 20% and 45% *vs*. 21%, respectively; p = 0.011 and p = 0.002, respectively) (Table 5).

The rates of complications also significantly differed based on the preoperative HbA1c level. Specifically, the rates of any complications and infectious complications were higher in patients with normal preoperative HbA1c

Table 2. Changes in maximum blood glucose levels on postoperative days 0-7

POD	mBGL (mg/dL)
POD 0	205 (182-234)
POD 1	185 (162-216)
POD 2	151 (137-169)
POD 3	162 (146-183)
POD 5	149 (133-171)
POD 7	147 (135-171)

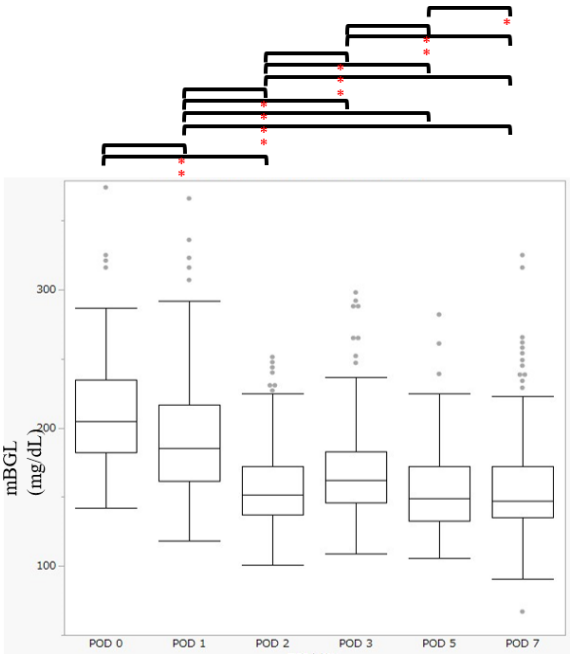

Figure 2. Changes in maximum blood glucose levels after esophagectomy from postoperative day 0 to 7 mBGL, maximum blood glucose level; POD, postoperative day. *p < 0.05 by Mann–Whitney *U* test.

Table 3. Maximum blood glucose levels on postoperative days 0-7 in patients categorized according to preoperative HbA1c levels

POD	HbA1c < 5.6 *n* = 43	HbA1c ≥ 5.6 *n* = 133	*p* value
POD 0	198 (198-217.5)	210 (186-237)	0.052
POD 1	179 (176-201.5)	191 (164-223)	0.022*
POD 2	147 (146.5-161.25)	154 (138-174)	0.057
POD 3	161.5 (161-181)	163 (146-182)	0.656
POD 5	145 (143-168)	150 (137-172)	0.164
POD 7	141 (140-159)	149 (137-172)	0.029*

*p < 0.05 by Mann–Whitney *U* test

Table 4. Maximum blood glucose levels on postoperative days 0-7 in patients with postoperative complications

Variables	Any complications (+) n = 114	Any complications (-) n = 62	*p* value
POD 0	213 (182-241)	202 (186-218)	0.206
POD 1	191 (162-221)	181 (161-208)	0.299
POD 2	154 (141-167)	144 (133-177)	0.42
POD 3	166 (149-186)	155 (143-175)	0.014*
POD 5	150 (136-176)	148 (131-165)	0.194
POD 7	149 (136-173)	142 (133-171)	0.122
	Infectious complications (+) *n* = 79	Infectious complications (-) *n* = 97	*p* value
POD0	215 (182-244)	202 (182-222)	0.236
POD1	195 (165-235)	181 (161-207)	0.067
POD2	154 (142-173)	148 (135-170)	0.245
POD3	170 (149-193)	156 (145-176)	0.009*
POD5	151 (137-178)	148 (131-167)	0.08
POD7	150 (136-175)	145 (134-170)	0.172
	Pneumonia (+) *n* = 47	Pneumonia (-) *n* = 129	*p* value
POD0	217 (191-241)	203 (181-232)	0.152
POD1	196 (167-238)	181 (161-213)	0.067
POD2	158 (143-181)	148 (136-167)	0.117
POD3	175 (157-198)	157 (144-176)	< 0.001*
POD5	152 (140-185)	149 (131-168)	0.063
POD7	150 (135-176)	147 (135-171)	0.241

*p < 0.05 by Mann-Whitney *U* test

Table 5. Rates of postoperative complications in patients categorized according to maximum blood glucose levels on postoperative days 0-7

POD	mBGL (mg/dL)	Any complications (+) *n* = 114 (%)	Any complications (-) *n* = 62 (%)	*p* value
POD 0	<180	31	15	
	≥180	83	47	0.665
POD 1	<180	48	31	
	≥180	66	31	0.314
POD 2	<180	94	48	
	≥180	20	14	0.419
POD 3	<180	79	49	
	≥180	35	13	0.166
POD 5	<180	92	52	
	≥180	22	10	0.603
POD 7	<180	95	53	
	≥180	19	9	0.709
POD	PBG (mg/dL)	Infectious complications (+) *n* = 79 (%)	Infectious complications (-) *n* = 97 (%)	*p* value
POD0	<180	22	24	
	≥180	57	73	0.641
POD1	<180	31	48	
	≥180	48	49	0.174
POD2	<180	63	79	
	≥180	16	18	0.777
POD3	<180	50	78	
	≥180	29	19	0.011*
POD5	<180	63	81	
	≥180	16	16	0.520
POD7	<180	64	84	
	≥180	15	13	0.314
POD	PBG (mg/dL)	Pneumonia (+) *n* = 47 (%)	Pneumonia (-) *n* = 129 (%)	*p* value
POD0	<180	11	35	
	≥180	36	94	0.619
POD1	<180	16	63	
	≥180	31	66	0.081
POD2	<180	36	106	
	≥180	11	23	0.407
POD3	<180	26	102	
	≥180	21	27	0.002*
POD5	<180	35	109	
	≥180	12	20	0.127
POD7	<180	37	111	
	≥180	10	18	0.127

*$p < 0.05$ by chi-square or Fisher's exact test

levels (< 5.6%) than in those with high HbA1c levels (≥ 5.6%) (79% *vs*. 60% and 65% *vs*. 38%, respectively; $p = 0.024$ and $p = 0.002$, respectively) (Table 6). Additionally, the rate of pneumonia was higher in patients with normal HbA1c levels (< 5.6%) than in those with high HbA1c levels (≥ 5.6%), although the difference was not statistically significant (34% *vs*. 21%, $p = 0.073$).

Risk factors for infectious complications

Logistic regression analysis was performed to examine risk factors for infectious complications. Univariate analysis (Table 7) revealed that male sex, ASA-PS score > 3, HbA1c level < 5.6%, tumor in upper thoracic esophagus, surgical time > 590 min, blood loss > 220 mL, and nonthoracoscopic surgical approach were significantly predictors of infectious complications ($p = 0.008$, $p = 0.004$, $p < 0.001$, $p = 0.044$, $p < 0.001$, $p = 0.022$, and $p = 0.018$, respectively). Multivariate analysis including these factors revealed that age > 69 years (odds ratio [OR] 2.13, 95% confidence interval [CI] 1.01–4.49), ASA-PS score > 3 (OR 2.40, 95% CI 1.07–5.36), HbA1c level < 5.6% (OR 3.03, 95% CI 1.35–6.79), and operative time > 590 min (OR 3.05, 95% CI 1.47–6.33) were independent risk factors for infectious complications after esophagectomy (Table 8).

Table 6. Rates of postoperative infectious complications in patients categorized according to preoperative Hb A1c values

Variables	HbA1c < 5.6 *n* = 43	HbA1c ≥ 5.6 *n* = 133	*p* value
Any complications			
(+)	34	80	
(-)	9	53	0.024*
Infectious complication			
(+)	28	51	
(-)	15	82	0.002*
Pneumonia			
(+)	16	31	
(-)	27	102	0.073

*$p < 0.05$ by chi-square or Fisher's exact test

Prognosis

There was no significant difference in overall survival and relapse-free survival between the patients with high and low HbA1c values (Supplemental Figures S1, S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=79*).

Discussion

In this retrospective study elucidating the association of BG markers with perioperative complications after esophagectomy, the rate of infectious complications was higher in patients with preoperative HbA1c levels of < 5.6% than in those with preoperative HbA1c levels of ≥ 5.6%, although the mBG levels were lower in the former group than in the latter group. This is the first study reporting that a lower preoperative HbA1c is a risk factor for infectious complications after esophagectomy.

Many studies have demonstrated the association of perioperative hyperglycemia with morbidity and mortality (*4-7*). HbA1c is a useful marker to evaluate the status of diabetes treatment. Most studies reported that higher HbA1c levels were associated with higher rates of postoperative infectious complications and prognosis (*8,9*). However, various studies reported higher rates of

Table 7. Univariate analysis of factors predicting infectious complications

Variables	Odds ratio (95% CI)	*p* value
Age (years)		
≥69	1.33 (0.73-2.44)	0.341
Male	3.08 (1.30-7.29)	0.008*
Body mass index (kg/m^2)		
≥20.6	0.69 (0.37-1.29)	0.249
PS (ECOG)		
≥2	0.66 (0.30-1.49)	0.320
History of smoking	1.61 (0.72-3.59)	0.246
Comobidities		
Diabetes mellitus	1.08 (0.49-2.42)	0.858
Hypertension	1.35 (0.74-2.47)	0.334
Pulmonary disease	2.11 (0.86-5.16)	0.098
PS (ASA)		
≥3	1.98 (1.02-3.82)	0.004*
CCI		
≥5	1.70 (0.93-3.10)	0.081
Preoperative laboratory findings		
HbA1c (%)		
≥5.6	0.37 (0.18-0.77)	< 0.001*
Albumin (mg/dL)		
≥3.7	1.32 (0.68-2.57)	0.412
Prealbumin (mg/dL)		
≥26	1.55 (0.85-2.82)	0.150
Hemoglobin (g/dL)		
≥10.5	1.48 (0.72-3.05)	0.285
PNI		
≥48	1.48 (0.81-2.72)	0.202
CONUT		
≥4	0.77 (0.35-1.69)	0.518
Tumor location		
Ut	2.01 (1.01-4.00)	0.044*
TNM (UICC 8th)		
cT		
≥3	0.89 (0.48-1.65)	0.710
cN		
≥2	1.06 (0.51-2.19)	0.884
cM		
+	1.06 (0.34-3.28)	0.924
cStage		
≥III	1.00 (0.55-1.82)	0.988
SCC	1.31 (0.54-3.21)	0.552
Preoperative treatment		
+	0.76 (0.42-1.38)	0.362
Operation time (mins)		
≥590	3.01 (1.58-5.74)	< 0.001*
Blood loss (mL)		
≥220	2.02 (1.11-3.70)	0.022*
VATS approach	0.43 (0.21-0.87)	0.018*
Laparoscopic approach	0.76 (0.42-1.39)	0.377
Three-field lymphadectomy	0.78 (0.41-1.48)	0.450

*$p < 0.05$ by logistic analysis

Table 8. Multivariate analysis of factors predicting infectious complications

Variables	Odds ratio (95% CI)	*p* value
Age (years)		
≧69	2.13 (1.01-4.49)	0.046
Male	2.46 (0.93-6.52)	0.070
PS (ASA)		
≧3	2.40 (1.07-5.36)	0.034
HbA1c (%)		
<5.6	3.03 (1.35-6.79)	0.007
PNI		
≧48	1.66 (0.80-3.44)	0.202
Operation time (min)		
≧590	3.05 (1.47-6.33)	0.003
VATS approach	0.49 (0.22-1.07)	0.076

*$p < 0.05$ by logistic analysis

perioperative complications and worse prognosis even in patients with lower HbA1c levels and no diabetes (*14-16*). In the present study, we found higher mBG levels after esophagectomy even in the absence of diabetes and higher rates of infectious complications, reflecting perioperative stress hyperglycemia. Patients without a history of diabetes or those with high HbA1c levels had worse morbidity and mortality compared to those with known diabetes (*10*).

Studies show that the etiology of perioperative stress hyperglycemia is multifactorial (*17*). More invasive surgery, general anesthesia, anesthetic agents, glucocorticoids, higher body mass index, and higher HbA1c levels are known predictors of stress hyperglycemia (*18*). In most patients undergoing emergency surgery, the diabetes status of the patient cannot be determined due to time limitations. In these patients, managing perioperative stress hyperglycemia to prevent infectious complications can be challenging. However, in the present cohort, almost all patients had undergone screening for diabetes through BG and HbA1c measurements at the time of diagnosis and neoadjuvant therapy for esophageal cancer prior to esophagectomy.

Kotgal found that insulin was underused in patients without diabetes and hypothesized that hyperglycemia indicated higher stress levels in these patients compared to those with diabetes (*19*). In our institution, an identical protocol for hyperglycemia was used to manage both those with and without diabetes. Specifically, continuous insulin therapy was performed using an insulin pump in patients with BG levels of > 150 mg/dL to achieve BG levels of < 150 mg/dL. Future studies should investigate the timing of insulin infusion therapy initiation in patients with higher BG levels depending on the presence of diabetes.

Transient insulin resistance and impaired insulin signaling, which appear to contribute to perioperative hyperglycemia in patients with and without diabetes, are considered to be due to circulating proinflammatory cytokines and counter-regulatory hormones. Thorell reported that insulin sensitivity decreased an average of 50% for up to five days in the immediate postoperative period, with a normalization period of 9–21 days following surgery (*20,21*).

Esophagectomy is considered one of the more invasive surgical procedures employed in patients with gastrointestinal cancer. Infectious complications such as postoperative pneumonia and anastomotic leakage are considered critical factors for poor prognosis (*3,22*). In particular, postoperative pneumonia is a significant

prognostic factor after esophagectomy. During the intraoperative and perioperative periods, we often experienced hyperglycemia due to the high degree of stress and intraoperative injection of methylprednisolone to prevent acute respiratory distress syndrome. Perioperative control of high BG levels is important to prevent infectious complications. The American Diabetes Association recommends the control of postoperative BG levels with a target between 140 and 180 mg/dL (*23*). Furthermore, control measures should be implemented for both hyperglycemia and hypoglycemia. Not only hyperglycemia but also perioperative hypoglycemia is associated with ICU mortality (*11,24-26*). The importance of BG control during the first week after gastrointestinal and vascular surgery has been extensively investigated. While the higher perioperative risk associated with hyperglycemia is well recognized, studies also show that hyperglycemia in patients without a history of diabetes increases perioperative mortality.

On the other hand, morbidity and mortality associated with diabetes cannot be fully explained by higher preoperative HbA1c levels. Studies focusing on other risk factors reported that BG variability was associated with complications. Koga described that BG variability was associated with pneumonia and that BG level was an independent poor prognostic factor in patients with esophageal cancer (*4*).

Continuous glucose monitoring is useful for hyperglycemia in the perioperative period (*26,27*). In recent years, artificial pancreas therapy has been used to control both hyperglycemia and hypoglycemia and its utility has been demonstrated in some surgical procedures. We also used artificial pancreas for poorly controlled cases (*28*).

The technologies to utilize insulin therapy for hyperglycemia are still evolving, with various guidelines recommended by academic societies across the globe. Furthermore, perioperative BG control is performed not only by surgeons and nurses but also by medical care teams (*20*).

Studies evaluating the relationship between BG levels and infectious complications after esophageal surgery reported that BG levels up to POD 3 were associated with pneumonia and that the average BG level on PODs 3 and 5 was a predictive factor for infectious complications (*4-7*). BG levels might initially increase due to the invasion prior to pneumonia or other infectious complications. The knowledge that changes in BG precede systemic complications is a clinically important finding that may be utilized for effective preventive interventions.

Although the causal relationship between high PGL and pneumonia is unclear based on the current study findings, effective postoperative BG control may reduce the rate of infectious complications, especially pneumonia, and may be considered a good predictor of pneumonia. In cardiovascular surgery, the reported rate of hypoglycemia is 7.5–21.4% in patients with controlled BG levels of <150 mg/dL (*24-26*). In the current cohort, the rate of hypoglycemia was approximately 11%, comparable to that reported in previous studies. Some studies reported that hypoglycemia was associated with mortality and composite outcomes in patients in the ICU. In the present study, the rate of all postoperative complications was not higher in hypoglycemic patients compared to hypoglycemic patients, which might be due to the effective initiation of insulin infusion therapy in the early phase of the ICU stay.

Two factors might explain the relatively low HbA1c. HbA1c is an indicator for long-term BG control in the previous 8–12 weeks, and a low HbA1c level suggests malnutrition and anemia. In fact, our analyses revealed that a low HbA1c level of < 5.6% was significantly associated with anemia, low albumin level, and low prognostic nutritional index score ($p < 0.05$ for all) (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=79*). In the present study, we found that low preoperative HbA1c levels were associated with not only nutritional markers but also anemia due to bone marrow suppression resulting from preoperative treatment. Although these factors were not direct independent risk factors for infectious complications, they may be combined indicators of nutrition and anemia.

The present study has several limitations that should be acknowledged. First, this was a retrospective observational study including a small cohort and was conducted in a single institution; therefore, the possibility of selection bias remains and future studies with larger cohorts are necessary to confirm our findings. Second, the BG levels were determined using samples obtained from arteries or veins. Previous studies reported that BG levels determined using samples from arteries and veins differed and that the accuracy decreased slightly in patients with hyperglycemia (*29-31*). The methods used to measure BG varied depending on the patient's length of stay in the ICU, which might have had some impact on the study findings. Finally, many hormones and cytokines can be involved in perioperative hyperglycemia. Future studies should investigate the relationship of such factors with BG markers in the context of perioperative complications after esophagectomy.

In summary, in the present study investigating the relationship of BG markers with perioperative complications after esophagectomy, we found that the rate of infectious complications was higher in patients with HbA1c levels of < 5.6% than in those with HbA1c levels of ≥ 5.6%. This is the first study to report a lower preoperative HbA1c level as a risk factor for infectious complications after esophagectomy.

Acknowledgements

They would also like to thank Orino Tomomi for the data sampling and Enago for the English language review.

Funding: This work was supported by grants from the National Center for Global Health and Medicine (26-117, 29-1019, 20A1017 and 23A2013).

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

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Received November 13, 2023; Revised March 14, 2024; Accepted March 20, 2024.

Released online in J-STAGE as advance publication March 28, 2024.

Address correspondence to:
Kazuhiko Yamada, Department of Surgery, National Center for Global Health and Medicine, 1-21-1 Toyama Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: kayamada@hosp.ncgm.go.jp

Global Health & Medicine. 2024; 6(3):199-203.
ORIGINAL ARTICLE
DOI: 10.35772/ghm.2024.01019

Comparison of oncological outcomes of upfront androgen receptor signaling inhibitors and combined androgen blockade in Japanese patients with metastatic castration-sensitive prostate cancer

Michio Noda, Taketo Kawai*, Kanade Hagiwara, Takahiro Yoshida, Kazuki Yanagida, Yuumi Tokura, Itsuki Yoshimura, Tomoyuki Kaneko, Tohru Nakagawa

Department of Urology, Teikyo University School of Medicine, Tokyo, Japan.

Abstract: In recent years, randomized controlled trials have demonstrated that upfront androgen receptor signaling inhibitors (ARSIs) prolong overall survival (OS) compared with androgen deprivation therapy (ADT) alone or combined androgen blockade (CAB) in patients with metastatic castration-sensitive prostate cancer (mCSPC). However, it remains unclear whether upfront ARSI is superior to CAB in Asian populations, among which the efficacy of ADT/CAB is considered relatively high. In this study, we compared the oncological outcomes of upfront ARSI and CAB in Japanese patients with mCSPC. Patients with mCSPC who underwent systemic therapy between May 2009 and October 2023 were enrolled retrospectively. Propensity score matching (PSM) was performed to compare the castration-resistant prostate cancer-free survival (CRPC-FS), cancer-specific survival (CSS), and OS between patients treated with upfront ARSI (ARSI group) and those treated with CAB (CAB group). In total, 30 and 142 patients were enrolled in the ARSI and CAB groups, respectively. After PSM (25 patients in each group), CRPC-FS was significantly longer in the ARSI group than in the CAB group (median: 36.7 *vs.* 12.3 months, hazard ratio: 0.44, 95% confidence interval: 0.20–0.97, $p = 0.035$). No significant differences were observed in CSS or OS between the two groups. In conclusion, when compared to CAB, upfront ARSI might have the potential to extend CRPC-FS among individuals in the Japanese population.

***Keywords*:** castration-sensitive prostate cancer, androgen receptor signaling inhibitors, combined androgen blockade, castration-resistant prostate cancer-free survival, propensity score matching

Introduction

Prostate cancer is a predominant oncological concern among men in Japan and worldwide. Although the incidence and mortality rates of prostate cancer in East Asian populations are reported to be less than half of those in Caucasian and African-American populations (*1*), Japan has witnessed a notable increase in prostate cancer cases, reaching 9,474 in 2019, more than double the number of 5,399 deaths recorded in 1995 (*2*). As life expectancy increases, more patients are being diagnosed with metastatic prostate cancer at the time of initial diagnosis. The standard treatment for patients with metastatic castration-sensitive prostate cancer (mCSPC) has been androgen deprivation therapy (ADT), either by medical or surgical castration. However, many patients develop castration-resistant prostate cancer (CPRC) and die several years after ADT initiation. Asian populations, including the Japanese, are generally more susceptible to ADT than Western populations (*3*). In Japan, combined androgen blockade (CAB) therapy using ADT in combination with anti-androgens has been used for the treatment of mCSPC since 2000. However, a phase III randomized controlled trial (RCT) comparing CAB with ADT alone showed that CAB prolonged overall survival (OS) compared with ADT alone for cT3-4 or cN1 prostate cancer, but showed no advantage for cM1 patients (*4*).

Recently, upfront treatment with androgen receptor signaling inhibitors (ARSIs), such as abiraterone (*5*), enzalutamide (*6*), and apalutamide (*7*), has been shown to prolong OS and progression-free survival (PFS) compared with ADT alone in several phase III RCTs and has become the standard treatment for mCSPC. As for RCTs comparing ARSI and CAB, ENZAMET trial showed that upfront enzalutamide prolonged OS and PFS compared with CAB, which is the combination of ADT and either bicalutamide, nilutamide, or flutamide (*8*). However, this trial did not enroll Japanese patients, and it is uncertain whether upfront ARSI will show superiority over CAB, even in Japanese patients for whom ADT/CAB is considered more effective than in

Western patients.

In this study, we retrospectively gathered data of Japanese patients with mCSPC and conducted a comparative analysis of efficacy of upfront ARSI and CAB using propensity score matching (PSM).

Materials and Methods

Patients

We conducted a retrospective study using the medical records of patients diagnosed with mCSPC and treated systemically at the Teikyo University Hospital between May 2009 and October 2023. The inclusion criteria consisted of patients newly diagnosed with prostate cancer and identified with metastasis through imaging studies, who underwent CAB or upfront ARSI. Exclusion criteria included patients who received treatments other than CAB or upfront ARSI, such as ADT alone or upfront docetaxel. A high/low volume of metastases was defined according to the CHAARTED criteria (*9*), and the extent of bone metastases was assessed using the extent of disease (EOD) score from bone scintigraphy. The criteria for defining CRPC included castrate levels of serum testosterone and evidence of disease progression, as indicated by imaging findings or elevation of prostate-specific antigen (PSA) levels. The determination of PSA worsening adhered to the definition provided by the Prostate Cancer Working Group 3 (*10*).

This study was approved by the Institutional Review Board of Teikyo University School of Medicine (no. 17-135-3), which waived the requirement for written informed consent due to the study's retrospective design. This study was conducted in compliance with the Declaration of Helsinki.

Treatment and assessment

Treatment was continued until PSA worsening, radiographic progression, or clinical progression. CRPC-free survival (CRPC-FS), cancer-specific survival (CSS), and OS were defined as the time from the initiation of treatment to CRPC, prostate cancer mortality, and all-cause mortality, respectively.

Statistical analyses

Differences in patient characteristics between the two groups were assessed using Student's *t*-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. CRPC-FS, CSS, and OS were evaluated using Kaplan–Meier curves and the log-rank test, with statistically significant differences defined as p value < 0.05. PSM was performed using the nearest-neighbor matching method with a caliper of 0.2, considering five covariates: initial PSA (iPSA), age, Eastern Cooperative Oncology Group performance status, grade group, and the CHAARTED criteria. Statistical analyses were performed using JMP Pro version 16.0.0.

Results

Patient characteristics

In total, 185 patients who underwent systemic treatment for mCSPC were enrolled in this study. Among them, we analyzed 30 patients who underwent upfront ARSI (ARSI group) and 142 patients who underwent CAB (CAB group) (Figure 1). Two patients who were initially treated with upfront docetaxel and 11 who received ADT alone were excluded from the analysis.

In the ARSI group, 14 patients received abiraterone (1,000 mg once daily), 11 received enzalutamide (160 mg once daily), and 5 received apalutamide (240 mg once daily), while all patients in the CAB group received bicalutamide (80 mg once daily). The clinicopathological characteristics of both the groups

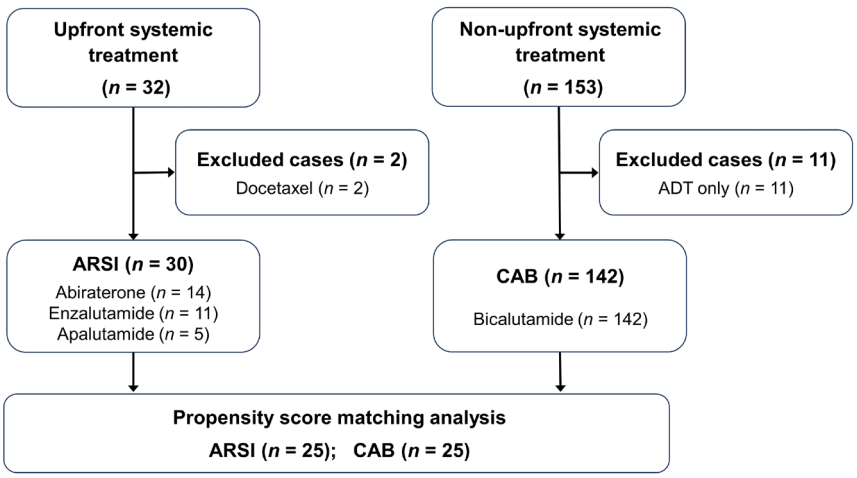

Figure 1. Flow chart of patient selection among mCSPC patients. mCSPC, metastatic castration-sensitive prostate cancer; ARSI, androgen receptor signaling inhibitor; CAB, combined androgen blockade.

are detailed in Supplemental Table S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=81*). The median follow-up period was 26.7 months (interquartile range [IQR]: 13.9–38.4 months) and 39.0 months (interquartile range: 22.1–68.1 months) in the ARSI and CAB groups, respectively.

Comparison of prognostic outcomes before PSM

Progression to CRPC occurred in 33% and 73% of patients in the ARSI and CAB groups, respectively, with a median CRPC-FS of 36.3 *vs*. 12.9 months (hazard ratio [HR]: 0.46, 95% confidence interval [CI]: 0.24–0.88, $p = 0.017$) (Supplemental Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=81*). Cancer-related death was observed in 13% and 43% of patients in the ARSI and CAB groups, respectively (median CSS: not reached *vs.* 71.6 months, HR: 0.65, 95% CI: 0.23–1.81, $p = 0.40$). Overall mortality rates were 23% and 58% in the ARSI and CAB groups, respectively, with median OS of 44.4 *vs.* 60.4 months (HR 0.81, 95% CI 0.37–1.79, $p = 0.60$). No adverse events of grade 3 or higher according to the Common Terminology Criteria for Adverse Events were reported in either group (data not shown).

Comparison of prognostic outcomes after PSM

Twenty-five patients in each group were matched using PSM. There were no significant differences in clinicopathological characteristics between the two groups after PSM (Table 1). In the matched cohorts, 36% and 88% of patients in the ARSI and CAB groups, respectively, progressed to CRPC, with median CRPC-FS of 36.7 *vs*. 12.3 months (HR: 0.44, 95% CI: 0.20–0.97, $p = 0.033$; Figure 2). Cancer-related death rates were 16% and 36% in the ARSI and CAB groups, respectively, with median CSS of 44.3 months *vs*. not reached (HR: 0.98, 95% CI: 0.28–3.44, $p = 0.98$). Overall mortality rates were 28% and 48% in the ARSI and CAB groups, respectively, with median OS of 44.3 *vs*. 78.7 months (HR: 1.59, 95% CI: 0.56–4.53, $p = 0.38$). Thus, although CSS and OS did not differ significantly between the two groups, CRPC-FS was significantly prolonged in the ARSI group.

Discussion

The results of this study indicate that upfront treatment with ARSI for mCSPC may be more beneficial than treatment with CAB in Japanese patients. Although no significant differences were observed in CSS or OS, the CRPC-FS was significantly longer in the ARSI group than in the CAB group. Furthermore, no severe adverse events were recorded in either treatment group, suggesting that upfront ARSI treatment was well tolerated.

Japanese patients respond better to ADT than patients of the Western populations. A retrospective study comparing prostate cancer mortality rates between Japanese and American patients receiving ADT as

Table 1. Baseline clinicopathological characteristics after PSM

Parameter	ARSI group ($n = 25$)	CAB group ($n = 25$)	p value
Age, years, median (range)	74 (55–86)	76 (62–84)	0.55[a]
Initial PSA, ng/mL, median (IQR)	420 (39–2683)	458 (65–3541)	0.29[a]
Hemoglobin, g/dL, median (IQR)	12.9 (11.3–14.0)	12.8 (11.0–13.5)	0.71[a]
ALP, IU/ml, median (IQR)	153 (80–294)	187 (94–399)	0.98[a]
LD, IU/L, median (IQR)	198 (177–291)	211 (178–339)	0.50[a]
ECOG PS, *n* (%)			
0	14 (56)	9 (36)	0.35[b]
1	10 (40)	14 (56)	
≥ 2	1 (4)	2 (8)	
Grade group, *n* (%)			
≤ 3	1 (4)	2 (8)	1.00[c]
≥ 4	24 (96)	23 (92)	
Metastatic site, *n* (%)			
Lymph node	18 (72)	17 (68)	1.00[c]
Bone	19 (76)	23 (92)	0.25[c]
Lung	8 (32)	4 (16)	0.32[c]
CHAARTED criteria, *n* (%)			
Low volume	7 (28)	8 (32)	1.00[c]
High volume	18 (72)	17 (68)	
EOD score, *n* (%)			
0	6 (24)	8 (32)	0.77[b]
1	3 (12)	2 (8)	
≥ 2	16 (64)	15 (60)	

[a]Student's *t*-test; [b]Chi-squared test; [c]Fisher's exact test. PSM, propensity score matching; ARSI, androgen receptor signaling inhibitors; CAB, combined androgen blockade; PSA, prostate-specific antigen; IQR, interquartile range; ALP, alkaline phosphatase; LD, lactate dehydrogenase; ECOG-PS, Eastern Cooperative Oncology Group performance status.

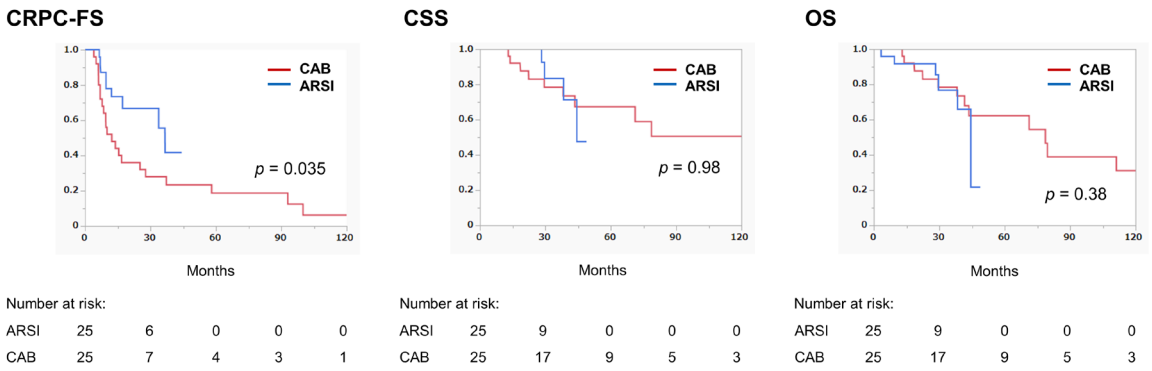

Figure 2. Comparisons of CRPC-FS, CSS, and OS between the ARSI and CAB groups (*n* = 25 each) after PSM. CRPC-FS, castration-resistant prostate cancer-free survival; CSS, cancer-specific survival; OS, overall survival; ARSI, androgen receptor signaling inhibitor; CAB, combined androgen blockade; PSM, propensity score matching.

primary therapy revealed that prostate cancer mortality in the Japanese patients was significantly lower than in the American patients, with a hazard ratio of 0.52 (*3*). Genetic disparities between races and differences in lifestyle factors such as diet may contribute to these variations. In addition, a multicenter retrospective analysis of Japanese patients showed that CAB treatment was more effective than ADT in prolonging PFS (*11*). Therefore, some opinions suggest that CAB is a sufficient treatment option, and that upfront treatment may not be necessary for mCSPC in Japanese patients.

Although no RCTs that compared upfront ARSI and CAB therapies in Japanese patients with mCSPC have been conducted, several retrospective studies have been reported (*12-16*). Ueda *et al. c*ompared matched cohorts of 28 patients each who received upfront abiraterone and CAB therapy, respectively, using PSM, demonstrating the superiority of upfront abiraterone in terms of OS and PFS (*12*). Similarly, Matsumura *et al.* compared matched cohorts of 63 patients each, who received upfront abiraterone and CAB therapy, respectively, using PSM and showed the superiority of upfront abiraterone in terms of OS and PFS (*13*). Conversely, Naiki *et al.* compared matched cohorts of 71 patients each, who received upfront abiraterone and CAB therapy, using PSM, finding upfront abiraterone to be superior in terms of PFS but not in terms of OS (*14*). Our results demonstrated the superiority of upfront ARSI over CAB in terms of CRPC-FS, but no superiority was observed in terms of CSS or OS, similar to the findings of Naiki *et al.* Recently, the J-ROCK Study, a large Japanese observational study comprising 974 patients, reported that upfront ARSI or docetaxel was superior to ADT or CAB in terms of PFS, CRPC-FS, and OS (*15,16*). Further validation in larger studies with longer follow-up periods is warranted to confirm the superiority of upfront ARSI over CAB in terms of CSS and OS in Japanese patients.

The present study has several limitations. First, the sample size was small and the follow-up duration was relatively short. These factors may have contributed to the lack of significant differences in CSS and OS. Second, this study was retrospective in nature. Despite performing PSM and matching to balance background factors, the reliability was inferior to that of an RCT.

In conclusion, based on our study utilizing PSM, there is an indication that upfront ARSI treatment may potentially extend CRPC-FS when compared with CAB in Japanese patients with mCSPC. Future efforts should involve accruing larger patient cohorts to further delineate the comparative efficacy of upfront ARSI and CAB therapies on CSS and OS.

Funding: None.

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

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Received February 28, 2024; Revised May 14, 2024; Accepted May 16, 2024.

Released online in J-STAGE as advance publication May 20, 2024.

**Address correspondence to*:
Taketo Kawai, Department of Urology, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8605, Japan.
E-mail: taketokawai@yahoo.co.jp

Global Health & Medicine. 2024; 6(3):204-211.
ORIGINAL ARTICLE
DOI: 10.35772/ghm.2024.01003

Updated information concerning trends in suicide rates in elderly in China, 2002–2020

Sanmei Wen[1,§], Xinyue Wang[2,§], Rongfeng Zhou[3], Tetsuya Asakawa[4,*]

[1] School of Journalism and Communication, Tsinghua University, Beijing, China;
[2] Xuhui District Center for Disease Control and Prevention, Shanghai, China;
[3] Admin Office, National Clinical Research Center for Infectious Diseases, the Third People's Hospital of Shenzhen, Shenzhen, China;
[4] Institute of Neurology, National Clinical Research Center for Infectious Diseases, the Third People's Hospital of Shenzhen, Shenzhen, China.

Abstract: The aim of this study was to investigate trends in suicide rates (SRs) among the elderly in China. Annual data on SRs among Chinese people ≥ the age of 65 were collected from China's Health Statistics Yearbook from 2002 to 2020. Then, data were stratified by age, region, and sex. Standardized SRs were calculated and analyzed using a conventional joinpoint regression model. Results revealed that overall, SRs among the elderly in China tended to decline from 2002–2020. Fluctuations in SRs, including in 2004–2005 due to the SARS epidemic, in 2009–2010 due to the economic crisis, and in 2019–2020 due to the COVID-19 pandemic, were also observed. Data suggested a relatively greater crude SR among the elderly (*vs.* young people), in males (*vs.* females), and in people living in a rural area (*vs.* those living in an urban area). SRs tended to rise with age. Joinpoint regression analysis identified joinpoints only for males ages 65–69 and over the age of 85 living in a rural area, suggesting that individuals in these groups are more sensitive to negative stimuli and more likely to commit suicide, necessitating closer attention. The findings from this study should help to make policy and devise measures against suicide in the future.

***Keywords*:** elderly, suicide, suicide rates, joinpoint, joinpoint regression model

Introduction

Suicide is not only a serious public health problem now but has also a serious social issue through the ages. It is a serious topic for those who have lost a loved one and also for personnel working in suicide prevention. Suicide is estimated to account for approximately 1.3% of all deaths worldwide, and most of those (77%) occurred in low- and middle-income countries (*1*). In general, the global suicide rates (SRs) tended to decline, but the problem of suicide among the elderly has been highlighted with the aging population. Indeed, the SRs among the elderly remain the highest in comparison those in other age groups (*2*). Studies from the different countries have found that the risk of suicide may increase with age (*2-4*), particularly among males (*5*). Globally, SRs among the elderly were approximately 16.17/100,000 among people ages 50–69 and 27.45/100,000 among people over the age of 70 in 2017 (*6*). The threshold of being elderly is commonly defined as ≥ the age of 65 (*7*). The problem of suicide among the elderly is a complex social problem, rather than a mere biological issue, that is influenced by a battery of social factors, such as allocation of social resources, social welfare policy, education, religion, cultural tradition, medical care, and family ties. Males over the age of 80 in particular are more likely to commit suicide because they are prone to have more physical and mental problems (*8*). Curtin *et al.* reported that the SRs in the US increased in 2021 (*9*), which might be attributed to the impact of the COVID-19 pandemic (*10*). In light of a study by De Leo, elderly in high-income countries enjoy good heath as well as a satisfactory social existence like younger people do, whereas the situation is quite different in low- and middle-income countries: the elderly seems to be excluded from active social participation (*7*). Accordingly, closer attention should be paid to the problem of suicide among the elderly in low- and middle-income countries, where SRs are deemed to be an important index.

The trends in suicide in China are in line with global trends. In general, SRs in China also tended to decline among all age groups (*11*), including the elderly population, males and females, and people living in a rural or urban area (*12*). The crude SR among males and females living in a rural area dropped from 15.24 to 9.58 and 15.40 to 7.16 per 100,000 people, respectively, from 2002 to 2015. SRs among males and females living in an urban area dropped from 13.16 to 5.85 and 12.40 to 4.27 per 100,000 people, respectively (*11*). This can reasonably be interpreted as the benefits of better

social welfare, better medical care, *etc*. as a result of urbanization due to economic growth in China. Previous studies reported marked sex differences in SRs in China (*11,13-15*). The most marked change was a rapid decline in the SR among women living in a rural area. Women, and particularly young women living in a rural area, reportedly had three major risks of suicide in the past, namely subordination in the family, conflicts, and the availability of pesticides (*13*). Hou *et al.* contended that the young women living in a rural area previously had a high SR because of many complex reasons such as stress, concepts of traditional culture (traditional gender roles according to Confucianism, humiliation, or shame), and family conflict (*14*). Suicide might be a way to deal against these factors (*11*). However, this situation changed with social development. Females in China were granted more opportunities, a higher income, and a higher status, which might be the main reasons for the decline in the SR. In addition, timely intervention in psychological strain may play a role in this decline (*15*). Nevertheless, SRs, and particularly those among the elderly, might sometimes fluctuate due to complex changes in social factors, *e.g.*, urbanization might act as a double-edged sword in influencing SRs (*13*). On the one hand, urbanization can bring better social services, while it can also bring stress and a heavier financial burden, easily affecting the elderly. Second, suicide among the elderly is also a noteworthy social problem in China. The elderly accounted for approximately 24% of all suicides before the 1980s in China (*16*). Nonetheless, after 2000s, their proportion dramatically increased to 79.19% (*16*). SRs among the elderly are highest in China and are approximately five times higher than the SRs among younger people (*17*). A recent study investigated the SRs among the elderly in China in 2003, 2008, 2013, and 2018 using an annual percentage change (APC) model. The results were highly complex: *i*) the risk of suicide also increased with age among the elderly living in a rural or urban area, *ii*) there were great fluctuations in both rural and urban areas during the years in question and in both males and females. The SR among the elderly living in an urban area was greater than that among less elderly living in a rural area (≤ the age of 70); however, the trend was reversed among the older elderly (> the age of 74, those living in a rural area > those living in an urban area) (*3*). The aforementioned studies provided limited information on the changes in SRs among the elderly in China since it only investigated four time points.

Based on previous studies (*3,11*) and findings, trends in SRs need to be stratified by sex, age, and region. Moreover, analyses over a relatively long period, involving the impacts of several important events such as outbreak of SARS in 2003, the economic crisis in 2008, as well as the potential impact of the COVID-19 epidemic, are helpful to gain a better understanding of the trends in SRs in China. Accordingly, the current study investigated the trends in SRs among Chinese elderly stratified by sex, age, and region using a joinpoint regression model often used to study SRs (*18*). In order to perform a comprehensive analysis, data were collected from 2002 to 2020. A more rigorous analysis was attempted to provide more detailed information regarding the trends in and the *status quo* of suicide among the elderly in China. The findings from study may help to gain a more comprehensive understanding, which is important for suicide prevention in the future.

Materials and Methods

Data collection

To analyze the potential impact of SARS in 2003, annual data on SRs from 2002 to 2020 (at the initiation of this study, data until 2020 were available) were collected from the China's Health Statistics Yearbook (CHSYB), which is based on the authoritative Ministry of Health Vital Registration (MOH-VR) System. Data in this MOH-VR system are deemed to be official Chinese data that are routinely submitted to the WHO (*11*). Data on SRs are officially stratified by sex, age, and region. Region is divided into urban and rural areas as per the official definition. Briefly, cities are urban while counties and towns are rural (*11*). In this study, only data on elderly were included. Here, "elderly" were defined as "people ≥ the age of 65" in line with the CHSYB as well as several previous analogous studies (*13,17,19*). Age was grouped as ages 65–69, ages 70–74, ages 75–79, ages 80–84, and ≥ the age of 85. Four stratified groups, namely males living in a rural area, females living in a rural area, males living in an urban area, and females living in an urban area, were created.

Statistical analysis

SR data were standardized using the Segi's World Standard Population (*20*). The age-adjusted SRs of the four groups were calculated. SRs in this study were specified as per 100,000 people per year. The probability of a type 1 error was maintained at 0.05.

The Poisson approximation method was used to calculate the age-specified standard error (*21*). Joinpoint regression analysis (Joinpoint Regression Program, Version 4.5.0.1) (*22*) was used to identify the changes in SRs. After performing a grid search, a permutation test, and using the Bayesian information criterion, the best-fitting combination of segments and joinpoints can be identified (*23*). Once the joinpoint was identified, the trend line was then divided into several segments with different slopes by joinpoint, indicating significant changes in the slope. In light of statistical criteria in the joinpoint model, the SRs are assumed to vary at a constant percentage at an estimated time and frequency. Therefore, the APC was calculated to characterize trends

in rates over time. The default value for the maximum number of joinpoints depends on the number of data points. In this study, the minimum number of points was set at 0, and the maximum number of joinpoints was set at 3 based on the grid search method (*24*). Likewise, the average annual percentage change (AAPC) was calculated as a weighted average of the APCs over a period including several years, which may summarize the trend over a pre-specified period. If the trend is unchanged, APC should be equal to AAPC.

Results

Figure 1 shows the crude SRs among Chinese elderly from 2002 to 2020. Figure 1A shows the trends in SRs stratified by age for these people. Broadly, the SRs in five groups from 2002 to 2020 tended to decline even though there were fluctuations in certain years. For example, there were marked increases in 2004–2005 and 2008–2010 among all groups, along with slight increase in 2006–2007 among all groups and in 2019–2020 among people ages 65–69, ages 70–74, ages 75–79, and ages 80–84. A point worth noting is that in 2008–2010, several groups (ages 80–84 and over the age of 85) exhibited a markedly higher SR (Figure 1A). Figure 1B shows the trends in SRs stratified by region and sex. Overall, the SRs were highest for males living in a rural area > females living in a rural area > males living in an urban area > females living in an urban area. Likewise, SRs tended to broadly decline for all groups from 2002 to 2020, though there were certain fluctuations particularly from 2002 to 2010. The crude SRs were 509.13 to 209.7 among males living in a rural area, 331.46 to 136.66 among females living in a rural area, 525.91 to 90.39 among males living in an urban area, and 316.78 to 65.08 among females living in an urban area (per 100,000 people, 2002 *vs.*2020). The highest reduction was among males living in an urban area (82.81%), whereas the lowest was among females living in a rural area (58.77%) (Figure 1B).

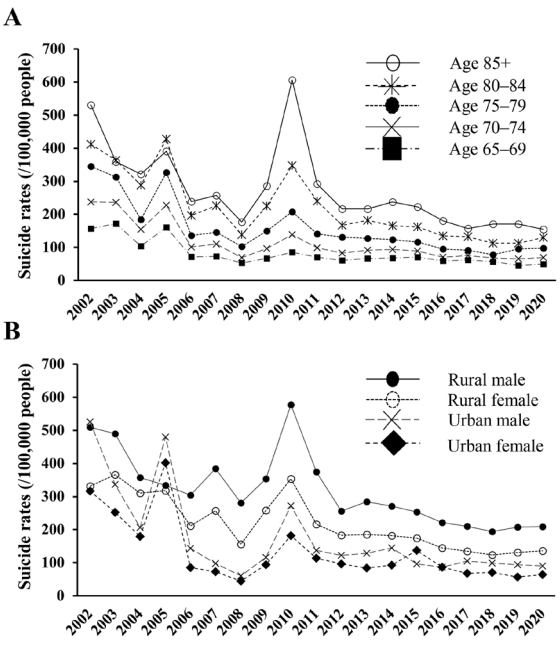

Figure 1. The crude suicide rates among Chinese elderly from 2002–2020. (A) Suicide rates among Chinese elderly stratified by age; **(B)** Suicide rates among Chinese elderly stratified by region and sex.

Figure 2 and Table 1 show the trends in standardized SRs among Chinese elderly stratified by age, region, and sex analyzed using a joinpoint regression model. A joinpoint was identified for only two groups, namely males over the age of 85 and those ages 65–69 living in a rural area. Three joinpoints were identified for males over the age of 85 living in a rural area; the trend line was divided into four linear segments (periods) with different slopes. The first period was 2002–2006, when the SR decreased 12.5%. The second period was 2006–2010, when the SR markedly increased (32.8% annual change), followed by a sharp decrease in the third period (2010–2013, 28.5% annual decrease). There was a gradual decline in the fourth period (2013–2020, 3.2% annual decrease). Nonetheless, the AAPC for this group was the lowest among all groups (3.5% average annual decrease). One joinpoint was identified for males ages 65–69 living in a rural area; the trend line was divided into two linear segments (periods). The first period was 2002–2006, when a sharp decline was evident (14.5% annual decrease). The second period was from 2006 to 2020, when a gradual decline occurred (3.2% annual decrease). No joinpoints were identified for the other groups (Figure 2). The data on APCs (equal to AAPCs) shown in Table 1 suggest that the greatest decline in the SR was 10.8% among males ages 75–79 living in an urban area, whereas the slightest decline was only 5.0% among females ages 80–84 living in a rural area (Table 1).

Discussion

The current study analyzed the trends in SRs among the elderly from 2002 to 2020 stratified by sex, age, and region using a conventional joinpoint regression model. Overall, SRs in both sexes and all age groups and regions have tended to decline, although there were certain fluctuations. *i*) Data suggested that the SR among older elderly was higher than that among younger elderly, namely the age of 85 > ages 80–84 > ages 75–79 > ages 70–74 > ages 65–69 (Figure 1A). *ii*) The SR among males was greater than that among females in the same region overall, particularly after 2006, namely males > females. *iii*) The SR among people living in a rural area was greater than that among people living in an urban area, namely people living in a rural area > people living in an urban area (Figure 2B). The joinpoint regression model revealed joinpoints only for males over the age of 85 and ages 65–69 living in a rural area, whereas no joinpoints were identified for

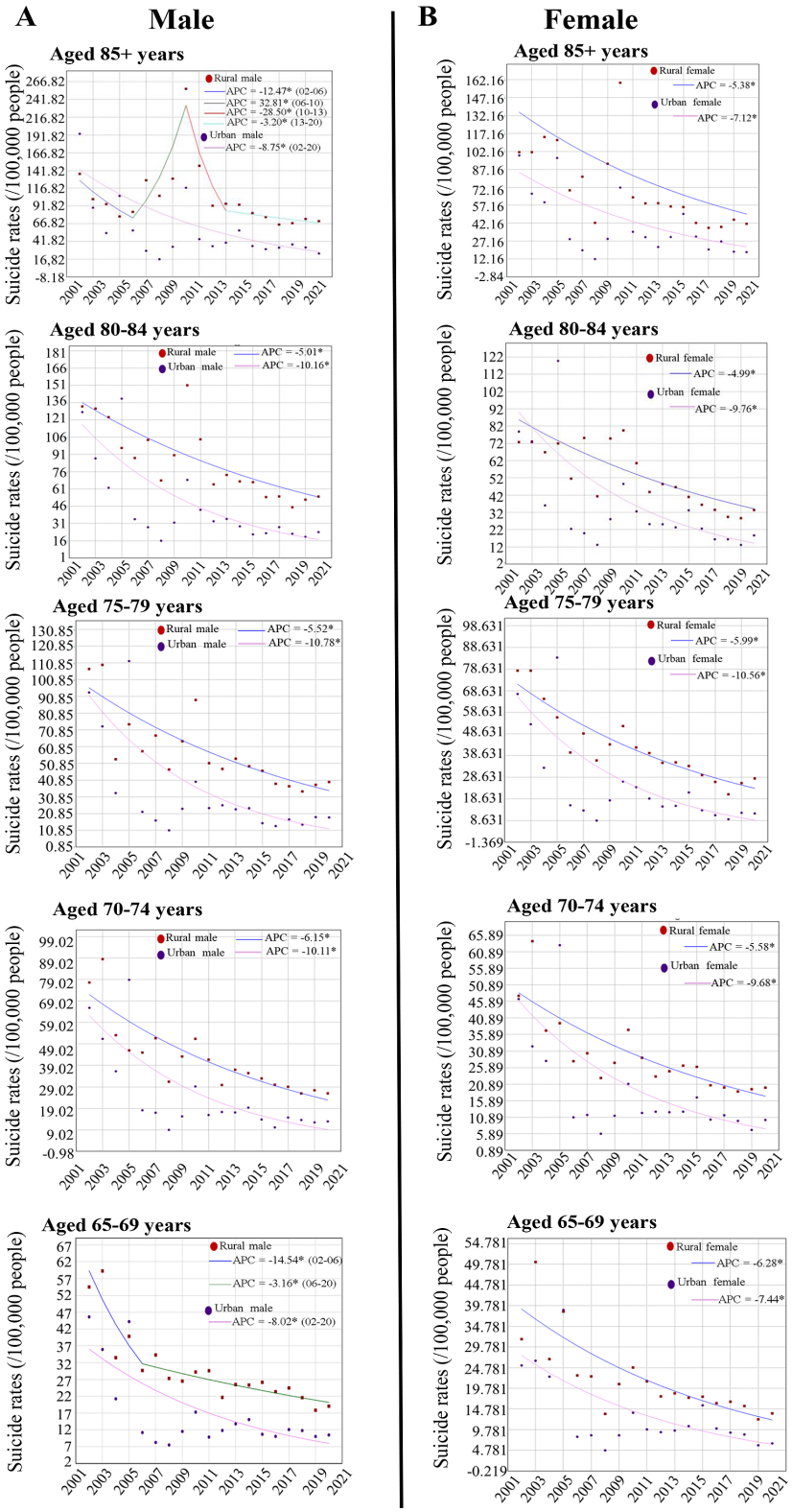

Figure 2. Standardized suicide rates stratified by age, region, and sex in Chinese elderly (over the age of 65) from 2002–2020, with line segments from joinpoint regression models. (A) Data on males: Three joinpoints were identified for males over the age of 85 living in a rural area, and one joinpoint was identified for males ages 65–69 living in a rural area; **(B)** Data on females. No joinpoints were identified.

the other groups (Figure 2 and Table 1). These results indicated that the trends in SRs among males living in a rural area were easily influenced by external factors. To the extent known, this is the first study using SR data over 19 years and focusing on the problem of suicide among the elderly in China. These findings could help to better understand the trends in and the *status quo* of the problem of suicide among the elderly in China and

Table 1. Joinpoint regression analysis of trends in suicide rates among Chinese elderly stratified by region and sex (per 100,000 people age 65 and over from 2002-2020)

Group Age	Segment 1		Segment 1		Segment 1		Segment 1		Entire range AAPC (95% CI)
	Period	APC (95% CI)	Period	APC (95% CI)	Period	APC (95% CI)	Period	APC (95% CI)	
Males living in a rural area									
65–69	2002-2006	-14.5 (-22.1, –6.2)	2006-2020	-3.2 (-5.2, –1.1)					-5.8 (-8.1, –3.5)
70–74	2002-2020	-6.2 (-7.8, –4.5)							-6.2 (-7.8, –4.5)
75–79	2002-2020	-5.5 (-7.4, –3.6)							-5.5 (-7.4, –3.6)
80–84	2002-2020	-5.0 (-7.3, –2.6)							-5.0 (-7.3, –2.6)
85+	2002-2006	-12.5 (-21.3, –2.7)	2006-2010	32.8 (18.1,49.4)	2010-2013	-28.5 (-56.4,17.2)	2013-2020	-3.2 (-7.6,1.4)	-3.5 (-10.7, –4.3)
Males living in an urban area									
65–69	2002-2020	-8.0 (-10.8, –5.2)							-8.0 (-10.8, –5.2)
70–74	2002-2020	-10.1 (-13.4, –6.7)							-10.1 (-13.4, –6.7)
75–79	2002-2020	-10.8 (-14.3, –7.1)							-10.8 (-14.3, –7.1)
80–84	2002-2020	-10.2 (-13.5, –6.7)							-10.2 (-13.5, –6.7)
85+	2002-2020	-8.8 (-12.4, –4.9)							-8.8 (-12.4, –4.9)
Females living in a rural area									
65–69	2002-2020	-6.3 (-8.1, –4.4)							-6.3 (-8.1, –4.4)
70–74	2002-2020	-5.6 (-7.2, –3.9)							-5.6 (-7.2, –3.9)
75–79	2002-2020	-6.0 (-7.2, –4.8)							-6.0 (-7.2, –4.8)
80–84	2002-2020	-5.0 (-7.0, –2.9)							-5.0 (-7.0, –2.9)
85+	2002-2020	-5.4 (-9.3, –1.3)							-5.4(-9.3, –1.3)
Females living in an urban area									
65–69	2002-2020	-7.4 (-10.6, –4.2)							-7.4 (-10.6, –4.2)
70–74	2002-2020	-9.7 (-13.2, –6.0)							-9.7 (-13.2, –6.0)
75–79	2002-2020	-10.6 (-14.0, –7.0)							-10.6 (-14.0, –7.0)
80–84	2002-2020	-9.8 (-13.4, –5.9)							-9.8 (-13.4, –5.9)
85+	2002-2020	-7.1 (-10.5, –3.6)							-7.1 (-10.5, –3.6)

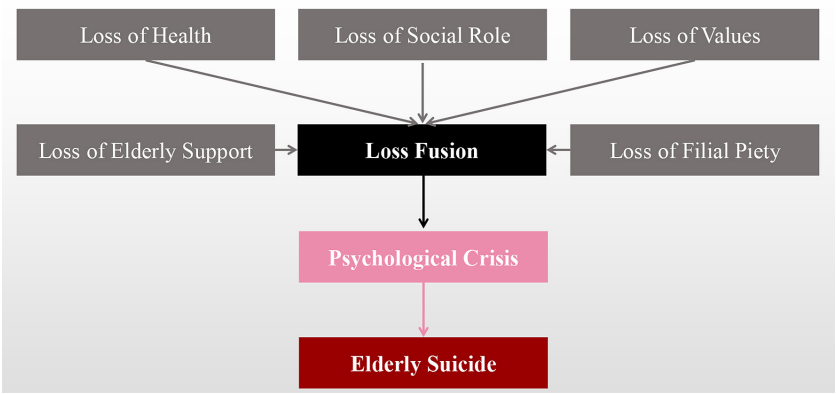

Figure 3. Diagram of the loss theory. Loss theory might be a plausible interpretation for suicide among the elderly. Loss of health, loss of one's social role, and loss of values can be considered personal loss, whereas loss of support and loss of filial piety can be considered social loss. Both personal loss and social loss comprehensively contribute to a psychological crisis in certain older individuals, resulting in self-abandonment and potentially leading to the worst outcome, namely suicide.

to make policy and devise measures to prevent suicide.

Interpretations

Overall trends

Suicide is a social problem rather than a pure biological/medical issue. Suicide is presumably influenced by many complicated social-biological factors, so investigation of the trends in SRs is a powerful tool. The overall downward trend is SRs in China since 2002 is in line with trends in countries such as Russia, Eastern European countries, and Japan (*18*) but differs from countries with rising SRs such as South Korea (*2*), the US, and the Philippines (*18*). The long-term decline in SRs in China is generally acknowledged to potentially be due to economic development (*25*) and urbanization (*13*), which mean better healthcare, insurance, pension systems, a more healthy lifestyle, *etc*. There were several fluctuations from 2002 to 2020. The most noticeable increase was in 2009–2010 and was noted among almost all ages (Figure 1A), both sexes, and all regions (Figure 1B). This short-lived rise was also noted in other countries, such as Greece, the Netherlands, and United Kingdom (*26*) and might be attributed to the global 2008 financial crisis, that is referred to as "a whole crisis effect" (*18*). The current data are the first to reveal such a "crisis effect" in China, which indicates that China is greatly affected by and part of "globalization". Another marked rise in 2004–2005 was not reported in the other countries. This increase might be attributed to the 2003 SARS epidemic that mainly affected China. A study from Hong Kong found that the SARS epidemic was associated with an increased SR among elderly females but not males or younger populations, which might be a result of a breakdown of social networks and limited access to health care (*27*). A slight rise was noted in 2019–2020, which might be associated with the advent of the COVID-19 pandemic. Unfortunately, at the point the current study was conducted, data on SRs in 2021, 2022, and 2023 in China were not available, thereby hampering further investigation of the influence of COVID-19, which will be included in a future study. Another slight rise was noted in 2006–2007, but a reasonable reason for this slight rise has yet to be found.

Old vs. Young

The current results indicated that SRs increased with age, which is in line with a previous study in China (*11*) and in the other countries (*8*). Li *et al.* attempted to explain this phenomenon with a "loss theory" (Figure 3). In light of this theory, aging is a social/physiological process, namely gradual but continuous loss of life resources including health, one's social role, and support. One can easily imagine how such social problems as well as physiological frailty (*28*) are increasingly aggravated with increasing age, resulting in a psychological crisis and ultimately potentially leading to suicide.

Male vs. Female

SRs were higher among males than females, which is in accordance with global trends, namely male SRs are over double those of female rates (*29*). One plausible interpretation is that older males in China usually have a heavier social/family burden and are easily affected by the sense of loss due to frailty as per Chinese cultural tradition. Moreover, analysis of standardized SRs with a joinpoint regression model identified joinpoints only for males living in a rural area, namely those ages 65–69 and those over the age of 85. These findings seem to imply that males are more "sensitive" to the influence of negative stimuli. Chang *et al.* found that SRs among males increased markedly due to the 2008 economic crisis (*26*). Kim *et al.* reported that SRs among males were rising markedly. All of these findings seem to imply that men are more sensitive to postretirement economic hardship (*2*). However, a study in Hong Kong yielded the reverse conclusion. Chan *et al.* found that the SARS epidemic in 2003 only increased suicide by older women; the SR among males was unchanged (*27*). Indeed, the social roles of males and females are

quite different among regions, due to differences in sex-related social recognition, cultural traditions, and economic roles. In this regard, the impact of suicide might be heterogeneous among different regions. The current data precluded an interpretation of crude trends in SRs among males and females from 2002–2006 and the crossover between males and females living in an urban area in 2015–2016, which are believed to be associated with the complex social and economic conditions at that time. A previous study in China also reported the existence of a reverse gap in 2006 (*11*). The study contended that improvement in the social status of women with social development in China might have contributed to a decrease in the SR among females (*11*). Accordingly, investigation of the sex differences in suicide should fully consider complicated sociopsychological factors, such as social status, culture, and incomes in the region.

Living in a rural area vs. living in an urban area

The current results suggested that people living in a rural area have a markedly higher SR than those living in an urban area, which may be due to the notable differences between urban and rural areas in China. Overall, older individuals living in an urban area are usually in a relatively better financial situation, have extensive insurance coverage, and have better access to medical care/care services in comparison to elderly individuals living in a rural area. Moreover, due to urbanization, many young people swarm into the city to make a living, and the older individuals left behind (elderly family members live in a rural area while the young family members live in an urban area) usually have to face loneliness and a lack of care. All these factors comprehensively influence the living conditions of the elderly in rural areas. Accordingly, the finding that elderly living in a rural area have a higher SR than elderly living in an urban area is plausible.

Strengths and Limitations

The current study had several strengths. First, continuous annual SR data were collected, allowing an analysis of trends annually. The influence of SARS (2003), the economic crisis (2008) and the potential influence of COVID-19 were evident. Second, data were stratified by age, region, and sex, and standardized SRs were calculated and analyzed using a conventional joinpoint regression model. Results revealed that males ages 65–69 and over the age of 85 living in a rural area were quite sensitive to negative impacts, necessitating closer attention.

Nonetheless, this study had several limitations. First, SR data were collected but other associated data such as financial data, data on medical care, and data on health insurance were not collected. This precluded a deeper investigation of the root causes of suicide, which are also important for suicide prevention. Second, SR data could not be obtained 2022 and 2023, so the impacts of COVID-19 on suicide could not be identified. All of these issues will be addressed in future research.

Measures based on the current findings and prospects for the future

Suicide is a global problem. Finding factors in which to intervene and then devising/implementing measures to intervene in these factors are the main tasks of suicide prevention. In light of the current findings, several measures have been proposed: Overall, the economic/mental problems of the elderly, and particularly males and those who are living in a rural area (and especially elderly family members who have been "left behind") are highly concerning. Better medical/psychological care should be instituted to provide timely medical/psychological intervention. Community- or family-based support should be advocated. Mood disorders, like depression and anxiety, should be promptly identified and dealt with. The current data indicated that males ages 65–69 and over the age of 85 living in a rural area were quite sensitive to negative impacts, which means both family members and social workers should pay attention to elderly individuals in these age groups and alleviate the negative influences on these people to the extent possible. In addition, according to a previous study indicating that educational campaigns might play a role in suicide prevention (*2*), community-based health education campaigns, should be conducted along with cultural campaigns. This may improve the knowledge of, awareness of, and responses to suicide and make people's lives more fulfilling, thereby improving their well-being and ultimately reducing suicide.

Conclusions

Overall, SRs among the elderly in China tended to decline from 2002 to 2020. Several fluctuations were noted, such as in 2004–2005 due to the SARS epidemic, in 2009–2010 due to the economic crisis, and in 2019–2020 potentially due to the COVID-19 pandemic. The overall trends in SRs were males > females, and people living in a rural area > people living in an urban area. Joinpoint regression analysis revealed joinpoints for males ages 65–69 and over the age of 85 living in a rural area, suggesting that these populations are potentially more sensitive to negative stimuli and thus require closer attention. The findings from this study could help with suicide prevention in the future.

Funding: This study was supported by the grants from the Shenzhen Fund to Build High-level Hospitals (grant no. 23274G1001) and the Shenzhen Science and Technological Foundation (grant no. JSGG20220606141001003).

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

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Received January 11, 2024; Revised April 1, 2024; Accepted April 18, 2024.

Released online in J-STAGE as advance publication April 21, 2024.

§*These authors contributed equally to this work.*
**Address correspondence to*:
Tetsuya Asakawa, Institute of Neurology, National Clinical Research Center for Infectious Diseases, the Third People's Hospital of Shenzhen, No. 29 Bulan Road, Shenzhen, Guangdong, China 518112.
E-mail: asakawat1971@gmail.com

Global Health & Medicine. 2024; 6(3):212-217.
DOI: 10.35772/ghm.2023.01100

Human papilloma virus (HPV)-related information acquisition and seeking behavior among infected women: A single center cross-sectional survey in Shanghai, China

Xiehua Yuan[1], Linlin Lu[1], Ruhe Jiang[1], Yue Yu[2], Jing Zhou[1,3,4], Ling Wang[1,3,4,*], Yan Du[1,3,*]

[1] Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China;
[2] Eight-year Clinical Medicine Program, Shanghai Medical College, Fudan University, Shanghai, China;
[3] The Academy of Integrative Medicine of Fudan University, Shanghai, China;
[4] Shanghai Key Laboratory of Female Reproductive Endocrine-related Diseases, Shanghai, China.

Abstract: Lacking of adequate knowledge is an obstacle to effective prevention of cervical cancer, yet factors that affect the information acquisition and seeking behavior as well as the information communication process are not well studied. We assessed information acquisition and seeking behavior, as well as perceived barriers of doctor-patient communication regarding human papilloma virus (HPV)-related information of infected women. Among 437 participants, 405 (93%) expressed demands for HPV-related information, while only a small proportion (100/437, 22.9%) actively sought information and felt obstacles comprehending. Web-based channels were most frequently utilized and medical personnel were the most trusted information source. Patients' satisfaction was significantly correlated with doctor's patience (r = 0.581, p < 0.001) and emotional caring (r = 0.555, p < 0.001). Compared to patients not actively seeking information, those actively seeking information were more likely to be single (p = 0.005), had higher education (p = 0.009) and monthly individual-level income (p = 0.023), and was more likely to undergo regular cervical cancer screening (p = 0.003), and were already or willing to be vaccinated (p = 0.008). The actively seeking information group also achieved higher scores in HPV knowledge test (p = 0.007). Public health interventions targeting HPV-infected women using specifically designed educational materials may influence information seeking behavior, increase HPV literacy and knowledge, which could potentially increase HPV vaccine uptake and cervical cancer screening rate.

***Keywords*:** HPV infection, information acquisition, health communication, cervical cancer, prevention

Introduction

Worldwide, cervical cancer ranks fourth of gynecologic malignancies among women and is a major cause of premature death (*1*). Approximately 95% of the cervical cancer cases are caused by chronic infection with certain types of carcinogenic human papillomavirus (HPV) (*2*). However, it is well recognized that first and secondary prevention are effective in preventing cervical cancer (*2*). Invasive cervical cancer can be prevented by HPV vaccination (*2*). Screening and removing precancerous lesions can prevent its further development into cervical cancer (*2*). In addition to health care accessibility and affordability (*3*), lacking of adequate knowledge is also an obstacle to the effective prevention of cervical cancer. It has been shown that worldwide women diagnosed with cervical intraepithelial neoplasia (CIN) do not have adequate knowledge about their disease, which affects their self-care ability as well as creates psychological stress (*4*). The burden of HPV-related health issues on the individual, family and society cannot be ignored. Therefore, it is important to precisely target high risk population and efficiently allocate health resource so as to achieve effective prevention and eventually improve women's health.

The importance of HPV-related information acquisition and dissemination

Health communication is crucial in primary and secondary prevention. Women with HPV infection are the vulnerable population that should be the major target of health communication and intervention. However, previous studies in developing countries mainly focused on the knowledge level and psychological evaluation of women infected with HPV (*5-7*), few have studied their information source, information seeking behavior, and how they comprehend and perceive the communication

and management of information by healthcare providers.

Identifying the factors that influence information acquisition and seeking behavior, as well as information dissemination processes, is critical to effectively communicate the correct HPV-related information to improve HPV vaccination and screening rates. This cross-sectional survey study was conducted to assess information acquisition and seeking behavior, as well as perceived barriers of doctor-patient communication regarding HPV-related information of infected women using a structured questionnaire (Supplementary Material, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=76*) at Obstetrics and Gynecology Hospital of Fudan University in Shanghai, China from July to October of 2019. The study protocol conformed to the ethical guidelines of the 2000 Declaration of Helsinki and was approved by the institutional review board at the hospital.

HPV-related information acquisition behavior

Overall, a total of 437 participants were included. Demographic characteristics and basic health status of the participants are presented in Supplemental Table S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=76*). The majority of the surveyed women considered themselves as either not having any knowledge (74/437, 16.9%) or limited knowledge (227/437, 51.9%) about HPV-related information. However, almost 93% (405/437) of the women expressed their demands for HPV-related knowledge (Supplemental Table S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=76*). Patients in general were interested in all aspects of HPV-related information, with "treatment strategies", "prevention strategies", and "symptoms after infection" obtaining more than 300 hits (Supplemental Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=76*).

Among 437 women participated, 100 (22.9%) of them actively searched information before 1st visit to the cervical clinic, while the majority (321/437, 73.5%) acquired some information passively. The trusted information source was evaluated using multiple choice questions with maximum of three options. Medical personnel (n = 369) was the most trusted source of information, followed by hospital WeChat (a popular social media app in China, which combines the functions of Facebook and Twitter) official account (n = 271); while radio (n = 13), community personnel (n = 20), and newspapers and magazines (n = 45) were the least trusted information source (Supplemental Figure S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=76*). It is not surprising that our study showed that medical personnel were the most trusted information source, since our population is a group of HPV-infected women seeking medical treatment at a tertiary hospital. Our study also showed that the credibility of the community resources was not well perceived, despite China's effort to improve the basic health infrastructure at the community level. A study from Jiangsu, a relatively rich province located at the east coast of China, reported that although substantial investments (human resources, materials, and financial) have been made to improve community health resources, the return is low (*8*). Community involvement is essential in cervical cancer prevention (*9*), and should be the forerunner of public health campaigns. However, in economically developed regions of China, patients tend to come to tertiary hospitals for primary health care instead of utilizing community health resources. It is crucial to appropriately educate patients, refine the referral system and increase the utilization of health care services at the community level, thus reducing the burden of tertiary hospitals.

Notably, fifty (11.4%) women expressed that they once had information avoidance behavior, and the common reasons for such behavior were: "knowing this information will cause anxiety" and "the information is too mixed and it is difficult to distinguish the truth". Among those patients (n = 100), 45 patients were not very sure about finding the right information, while 42 patients expressed a neutral level of assurance (Supplemental Table S3, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=76*). We further explored possible barriers, and found that major obstacles included information channels and information source credibility. Patients in general thought that there were obstacles when they actively seeking information (average score = 2.88) (Supplemental Table S4, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=76*). The most frequently used information channels were search engines and hospital WeChat official account, while the least used channels were seminars and community personnel (Supplemental Table S5, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=76*). This result is in line with the rapid development of information technology and corresponding information behavior change occurring in the Chinese society. Therefore, designing health educational materials should base on target's web-based health information seeking behaviors. It is helpful to understand how patients evaluate and choose the sources and more importantly, how they perceive their credibility and reliability (*10*).

Doctor-patient communication

Less than half (200/437, 45.8%) of the patients reported that they had around 4-5 min per visit to communicate with their doctors, which is acceptable at a tertiary hospital in China (*11*). The average score of patient satisfaction of the communication was 3.36, which was between neutral and relatively satisfied (Supplemental Table S6, *https://www.globalhealthmedicine.com/site/*

supplementaldata.html?ID=76). In general, the patients were satisfied with the doctor-patient communication.

We further evaluated the doctor-patient communication from three aspects: experience, effectiveness, and expectations (doctor behaviors that patients cared about) (Table 1). In general, the participants assessed their communication experience towards positive (average score all above 3). In terms of communication effectiveness, the average scores of cognitive, emotion, and behavior were all above 3, indicating a positive attitude. Especially for the behavior item, 315 (72%) participants chose completely accept treatment or preventive measures as recommended by the doctor. Overall, patients were concerned about doctors' behaviors during communication. The item they cared most was the tone; followed by facial expression, eye contact, and body language; and how the doctors ask questions. The correlation analysis showed that patient satisfaction of doctor-patient communication was significantly correlated with all aspects of communication experience, effectiveness, and expectation. Specifically, correlation coefficients indicated that there were relatively strong correlations with "during communication, the doctor was patient with me" and "during communication, the doctor cared about my feelings and emotions" (Supplemental Table S7, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=76*). Our results have suggested that patients' satisfaction was significantly correlated with doctor's patience and emotional caring, indicating possible improvement areas for interventions. Besides information materials, we should also take into account psychological factors such as patients' emotions and doctors' behaviors which will influence patients. In addition to improve doctor's communication skills, it is also of great importance to increase patient's health information literacy especially eHealth literacy (*12*), so precious time could be effectively spent in discussing more important issues.

It is found that the most frequently chosen channel by the patients in a hospital setting was WeChat official account (197 hits), followed by educational videos at the waiting area (182 hits); other frequently chosen channels included posters (162 hits), leaflets and brochures at the outpatient clinic (149 hits) (Figure 1). This time window (waiting period) should be used for efficient dissemination of cervical cancer and HPV related health educational materials. Qualified community health workers can come to the hospital and provide intervention (health education) for HPV-infected women during their waiting time, which could also greatly reduce the burden of tertiary hospitals and doctors, and facilitate doctor-patient communication. What is more, the educational materials should be concise and easy to understand for the lay population (*13*).

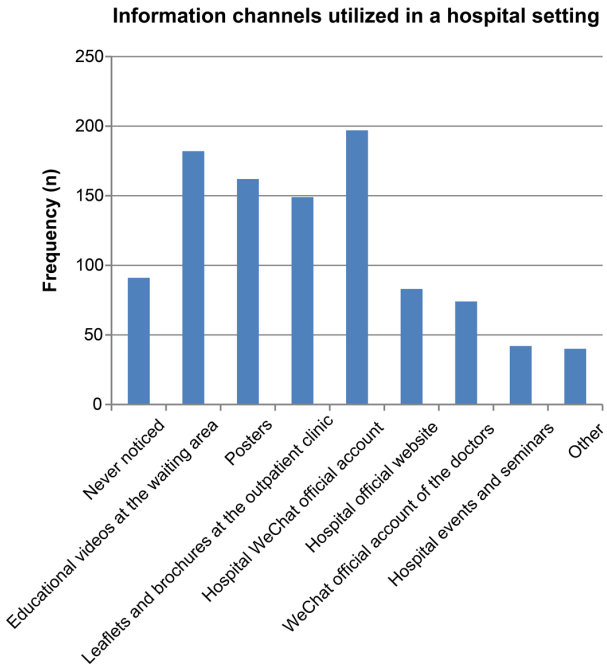

Figure 1. Information channels utilized in a hospital setting.

Table 1. Experience, effectiveness and expectation of doctor-patient communication (*n* = 437)

Item	Range	Mean ± SD
Experience		
The doctor communicated with me in a way that I could understand.	1-5	3.64 ± 1.01
During communication, the doctor cared about my feelings and emotions.	1-5	3.51 ± 1.04
The doctor fully explained the treatment plan.	1-5	3.56 ± 1.02
During communication, the doctor was patient with me.	1-5	3.49 ± 1.02
Effectiveness		
The communication helped me understand the information. (Cognitive)	1-5	3.67 ± 0.98
The communication alleviated my panic and stress. (Emotion)	1-5	3.61 ± 1.00
Would accept treatment or preventive measures of HPV as recommended by the doctor. (Behavior)	1-5	3.65 ± 0.61
Expectation		
Duration of time doctor spent in communication.	1-5	3.71 ± 0.98
How doctors ask questions.	1-5	3.91 ± 0.87
The doctors' tone during communication.	1-5	4.00 ± 0.89
The doctors' facial expression, eye contact, and body language, *etc.*	1-5	3.94 ± 0.94

Knowledge level, common misconceptions and attitudes

The following four aspects of HPV-related knowledge level were evaluated: general knowledge (Questions E1-6), risk factors (Questions E7-8), preventive measures (Questions E9-11), and HPV vaccine knowledge (Questions E12-13). The average score of the knowledge level was 6.48 ± 3.35 (range: -1 to 13). Our study found several common HPV misconceptions, which included "Q-E3. Most HPV infected persons have no symptoms (correct answer: Yes)", "Q-E9. Quit smoking and alcohol can prevent HPV infection (correct answer: Yes)", "Q-E11. There is effective drug treatment (correct answer: No)", and "Q-E12. Vaccine is still protective for those tested HPV positive (correct answer: Yes)" (Supplemental Figure S3A, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=76*). Those misconceptions may hinder doctor-patient communication and should be corrected before their meeting with the doctors. The attitudes towards vaccination (Questions E14-16) and screening (Question E17) are shown in Supplemental Figure S3B (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=76*). Studies of HPV literacy were mainly conducted in the United States, which have reported low to moderate HPV literacy (*14-15*). Despite differences in the study population and measurements of information literacy, our results were consistent, suggesting the urgency of improving HPV literacy.

Comparisons of patients with different information acquisition behaviors

We found that patients who actively seeking information had higher education level and monthly income, and were more likely to be single ($p < 0.05$ for all) (Table 2). This group of patients also had a higher percentage of undergoing regular screening ($p = 0.003$) and were already or willing to be vaccinated against HPV ($p = 0.008$) (Table 2). In addition, those patients achieved higher scores in knowledge question test ($p = 0.007$). In contrast, information seeking behavior was not associated with knowledge demands, or doctor-patient communication (Table 3).

Statistics have shown a rising trend of cervical cancer mortality rate among younger Chinese women (*16*). However, the vaccine coverage rate in China is low. A multicenter study of Chinese female college students showed that only 11% of the 4220 surveyed were vaccinated against HPV, and only more than half of those not receiving HPV vaccine expressed willingness (*17*). Furthermore, despite implementation of cervical

Table 2. Comparison of basic characteristics and health status between actively seeking information group and the other group (*n* = 437)

Variables	Active (*n*, %) *n* = 100	Not active (*n*, %) *n* = 337	*p* value
Age (years)			0.257
< 30	27 (27.0%)	83 (24.6%)	
31–40	45 (45.0%)	140 (41.5%)	
41–50	17 (17.0%)	88 (26.1%)	
≥ 51	11 (11.0%)	26 (7.7%)	
Education level			0.009
High school or lower	26 (26.0%)	118 (35.0%)	
Junior college	17 (17.0%)	91 (27.0%)	
College	43 (43.0%)	96 (28.5%)	
Graduate school	14 (14.0%)	32 (9.5%)	
Marital status			0.005
Married/ Cohabitation	75 (75.0%)	267 (79.2%)	
Single	20 (20.0%)	32 (9.5%)	
Other	5 (5.0%)	38 (11.3%)	
Monthly individual income [RMB]			0.023
< 2,499	17 (17.0%)	64 (19.0%)	
2,500–4,999	14 (14.0%)	84 (24.9%)	
5,000–9,999	31 (31.0%)	107 (31.8%)	
≥ 10,000	38 (38.0%)	82 (24.3%)	
Self-evaluated heath status			0.158
Very poor	1 (1.0%)	7 (2.1%)	
Relatively poor	9 (9.0%)	49 (14.5%)	
Average	57 (57.0%)	198 (58.8%)	
Relatively healthy	29 (29.0%)	79 (23.4%)	
Very healthy	4 (4.0%)	4 (1.2%)	
Screening for cervical cancer			0.003
On a regular basis	71 (71.0%)	182 (54.0%)	
Occasionally + Never	29 (29.0%)	155 (46.0%)	
HPV vaccine			0.008
Already/Will	67 (67.0%)	175 (51.9%)	
No/Not sure	33 (33.0%)	162 (48.1%)	

Table 3. Comparison of HPV knowledge, and patient-doctor communication aspects between actively seeking information group and the other group (n = 437)

Variables	Active n = 100	Passive n = 337	p value
Demands of HPV-related knowledge			0.117
No need at all	2 (2.0%)	2 (0.6%)	
Not very much	1 (1.0%)	1 (0.3%)	
Neutral	2 (2.0%)	24 (7.1%)	
In relative demand	41 (41.0%)	113 (33.5%)	
Great demand	54 (54.0%)	197 (58.5%)	
Variables of doctor-patient communication			
Satisfaction	3.5	3	0.253*
Experience	18	18	0.652*
Effectiveness	11	11	0.944*
Expectation	16	16	0.115*
Knowledge question scores	7.27 ± 3.35	6.25 ± 3.32	**0.007**

*Mann-Whitney U test p value.

cancer screening in women aged 35 to 64 years in rural areas since 2009, uptake of cervical cancer screening has not been evenly distributed and not yet achieved a satisfactory rate (*18*).

Conclusions and Suggestions

In the current study, we assessed the HPV-related information acquisition and seeking behavior among a group of HPV infected women who first visited the cervical clinic in a tertiary specialty hospital in Shanghai. We found that in general, those women expressed demands for every aspect of HPV-related information; however; only a small proportion of them actively sought information. In general, patients felt obstacles in comprehending the information, indicating less than optimal health information literacy.

To conclude, in this study we did not only evaluate "how the situation is", but also explored "what are the possible barriers and feasible intervention strategies". Public health interventions targeting HPV-infected women can redress misconceptions and may influence their information seeking behavior, increase HPV literacy and knowledge, which could potentially increase HPV vaccine uptake and cervical cancer screening rate. Our findings have provided evidence for developing more precise cervical cancer prevention and control strategies for the target population in Shanghai and also other cities in China.

Acknowledgements

The authors thank all women who participated in this study and filled in a questionnaire.

Funding: This work was supported by a grant from the Shanghai Talent Development Fund to Yan Du (Grant Number: 2017090). The funding agency had no involvement in study design, data collection, statistical analyses or interpretation of the results.

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

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Received September 15, 2023; Revised January 30, 2024; Accepted February 6, 2024.

Released online in J-STAGE as advance publication February 21, 2024.

Address correspondence to:
Yan Du, Obstetrics and Gynecology Hospital, Fudan University, No. 128 Shenyang Road, Shanghai 200090, China.
E-mail: sophiedu_61@163.com

Ling Wang, Laboratory for Reproductive Immunology, Obstetrics and Gynecology Hospital of Fudan University, 419 Fangxie Road, Shanghai 200011, China.
E-mail: Dr.wangling@fudan.edu.cn

DOI: 10.35772/ghm.2024.01027

"Fertility-friendly hospitals": A key measure to promote long-term and balanced population development in China

Jingyi Ma[1,2], Fei Ma[1,2,*], Heng Zou[1,2]

[1] Outpatient and Emergency Department, Xinhua Hospital Affiliated with the Shanghai Jiao Tong University School of Medicine, Shanghai, China;
[2] Institute of Hospital Development Strategy, China Hospital Development Institute, Shanghai Jiao Tong University, Shanghai, China.

Abstract: In response to the twin challenges of an aging population and declining birth rates, Zhejiang, China pioneered the concept of "fertility-friendly hospitals" in 2022 to support families and individuals in navigating the complexities of childbirth. Although fertility-friendly hospitals have not yet scaled up in number, their potential benefits and the challenges they face are evident. These facilities aim to provide comprehensive services from preconception to postnatal care, necessitating a high level of specialization and resource allocation, with an emphasis on patient education and participatory decision-making. Currently, there is an uneven distribution of resources across regions in China, with the density of maternal and child health care facilities in developed areas exceeding that of less developed regions by more than tenfold. The establishment of fertility-friendly hospitals will help to slow the pace of population aging and mitigate further declines in birth rates, thereby balancing the population composition and promoting long-term equitable social development. However, they also face challenges in balancing resources, improving the quality of services, and improving accessibility across different regions. As the concept is promoted and practiced, fertility-friendly hospitals are expected to become a significant force supporting China's population policy.

***Keywords*:** fertility rate, aging, maternal care, child health

Introduction

In recent years, significant shifts have occurred in the global demographic landscape, characterized by two prominent trends: population aging and declining birth rates. These trends are impacting social, economic, and health care systems. As the most populous country in the world, China is currently striving to deal with these social transformations. In this context, understanding the challenges brought about by population aging and declining fertility rates is crucial.

The international community is actively addressing the challenges posed by an aging population. According to a study published in the Lancet, human life expectancy is projected to increase gradually, with the global population reaching its zenith before the end of this century. Once the total fertility rate descends beneath the threshold of 1.5, the onset of a global population decline is anticipated to proceed in a sustained and inexorable manner (*1*). The array of strategies presently implemented by diverse nations is designed to modulate the trajectories pertaining to fertility rates, mortality rates, and migratory patterns (*2*). While the size and composition of the population are not factors that countries consider in their planning, they can be utilized to guide certain societal outcomes.

The aging and declining birthrate trends in China are particularly pronounced. Over the next twenty years, the issue of aging in China is projected to exacerbate, with densely populated metropolises facing more severe challenges. This demographic shift is anticipated to test the resilience of social security systems, health care, and the economy at large (*3*). China is transitioning from a period of a demographic dividend to one of a demographic burden, where the responsibilities of eldercare, social security expenditures, and government debt are expected to surge significantly. To address this issue, China must implement a raft of measures aimed at augmenting the birthrate. China has improved its fertility policies and provided moderate childcare support. The Chinese Government is incentivizing younger couples to have more children and it has established a more comprehensive childcare system, including facilities such as nurseries and kindergartens.

Concurrently, the Chinese Government has begun to underscore the necessity for health care systems and medical facilities to foster a supportive environment for families and individuals grappling with the complexities of fertility and family planning. The term "fertility-friendly hospitals" was coined in 2022 by the People's Hospital of Zhejiang Province, China, which pioneered an innovative approach to maternal and child health

care. The facility is seeking to create a comprehensive service model for maternal and infant health care and is committed to providing extensive health services for pregnant women and infants, thereby aiming to enhance the fertility rate (*4*).

The history of the development of fertility-friendly hospitals

The notion of "fertility-friendly hospitals," while having been explicitly conceptualized in the year 2022, is underpinned by a cadre of pre-existing, internationally recognized successful experiences and models, which serve as a valuable reference for health care facilities.

The first aspect is respecting the choices and wishes of pregnant and childbearing women. The University of São Paulo Clinical Hospital in Brazil has implemented a "humanized childbirth" program, offering a variety of birthing methods such as water birth, natural birth, and pain-free birth. This empowers expectant mothers to select the birthing method that best aligns with their physical condition and psychological needs (*5*). The autonomy of choice bolsters the agency and confidence of expectant mothers and also mitigates unnecessary medical interventions and complications, thereby enhancing both the safety and satisfaction associated with childbirth.

Second, the family should always be considered as a unit. Arkansas Children's Hospital in the United States implemented a "family-centered care" model by providing a familial inpatient environment (*6*). Parents and newborns can share the same hospital room, receiving 24-hour companionship services. These initiatives are intended to bolster emotional interactions and tactile engagement between parents and newborns, to encourage breastfeeding, and to facilitate the infant's early development, thereby reinforcing the bonds and sense of responsibility within the family unit.

Third, the provision of continuous health care is essential. The University College Hospital in London in the UK has consistently maintained a "community midwifery" program. By establishing a team of community midwives, the program offers comprehensive health services to pregnant and postpartum women, from pre-pregnancy to one year post-delivery (*7*). Such a framework fosters a stable patient-health care provider relationship, delivers personalized and professional health guidance and education, and facilitates the timely identification and management of various health issues, thereby reducing the rates of referrals and hospital admissions.

Fourth, the provision of diversified and innovative services is crucial. The Tokyo Women's Medical University Hospital in Japan has implemented a "fertility support" project, which incorporates experts and equipment from multiple fields such as assisted reproductive technology in human biology, genetics, and psychology. This initiative provides a variety of services for individuals facing fertility challenges or with special needs (*8*). Such measures cater to the reproductive requirements and preferences of diverse groups, aiding them in fulfilling their aspirations to conceive, thereby enhancing societal diversity and inclusiveness.

Fertility-friendly hospitals in China

The development of fertility-friendly hospitals in China is of paramount importance to the improvement of maternal and neonatal health outcomes. It plays a crucial role in fostering breastfeeding, improving the overall experience of childbirth, mitigating social disparities, and safeguarding the nation's rich cultural legacy. Such hospitals can bolster the health of mothers and infants by creating breast milk banks and disseminating knowledge on breastfeeding, thereby lowering the incidence and mortality rates of newborns, as well as diminishing the risks of childhood obesity, type 2 diabetes, breast cancer, and ovarian cancer (*9*). Fertility-friendly hospitals are committed to fostering an environment that is warm and respectful and also deeply supportive of the childbirth process, ensuring a nurturing setting for both mother and child. This helps to alleviate the anxiety of expectant mothers and bolster their confidence in childbirth. By offering a more diverse range of services, these hospitals can somewhat narrow the gap between pregnant women from varying socioeconomic backgrounds. In addition, China's obstetric practices are distinguished by their deep historical roots, which include traditional Chinese post-natal treatment and specific dietary habits. The creation of fertility-friendly hospitals in China facilitates the harmonious blending of these enduring traditions with contemporary medical practices, thereby guaranteeing their perpetuation (*10*).

The extensive development of fertility-friendly hospitals in China has not yet come to fruition. Nonetheless, a partial comprehension of the pertinent circumstances within the country may be gleaned by examining the state of maternal and child health care facilities, as well as the provision of maternity health care, across diverse locales.

According to the China Health Statistics Yearbook 2022, the distribution of medical personnel in maternal and child health care facilities in China in 2021 was as follows: 39.34% in the eastern region, 29.46% in the central region, and 31.2% in the western region (*11*). Moreover, disregarding factors such as educational background, professional titles, and years of service, there is a certain imbalance in the distribution of medical manpower in maternal and child health care facilities. This imbalance is primarily evident in the disparities between urban and rural areas. Such disparities are detrimental to the achievement of equitable and accessible fertility services.

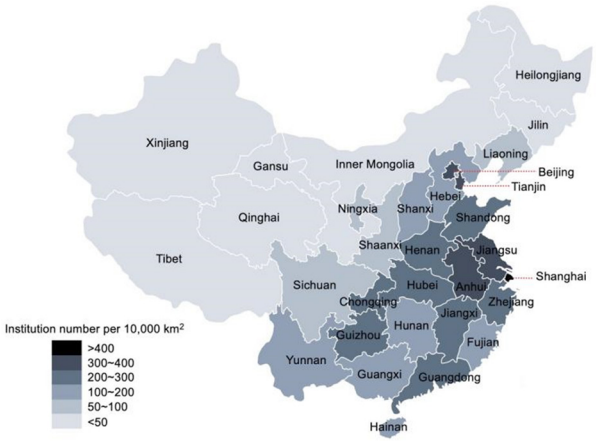

Figure 1. The distribution of maternal and child health care facilities in the Chinese Mainland in 2021. Excluding Hong Kong, Macau, Taiwan, and other archipelago, the distribution density of maternal and child health care facilities in major provincial-level administrative units of China is depicted here. Darker colors indicate a higher distribution density. Data source: *Ref.11*.

In general, the state of maternal health care across various regions in China is satisfactory, with extensive coverage of maternal health care. However, there are minor regional disparities that necessitate further augmentation and optimization of services. Overall, as indicated in Figure 1, the density distribution of maternal and infant health care facilities in China is demarcated by the Heihe-Tengchong Line from Heilongjiang to Yunnan. Density is higher in the east than in the west and higher in the south than in the north. Taking Shanghai and Xinjiang as examples, the total number of facilities in Xinjiang exceeds that in Shanghai, but the density of maternal and infant health care facilities in Shanghai is more than tenfold that in Xinjiang.

On one hand, the disparities in population distribution between the east and west lead to differing needs for maternal and infant health care; the southeastern coastal areas, being densely populated, have relatively comprehensive maternal and infant health care. On the other hand, the stark contrast in levels of economic development between these regions results in significant differences in the dissemination of advanced medical health care concepts and the implementation of supportive measures. The distribution of maternal and infant health care facilities and medical personnel is inextricably linked. In the western regions of China, challenging transportation conditions, higher altitudes, and limited communication with the outside world, coupled with the large seasonal temperature variations and relatively harsh natural conditions of the northern areas at high latitudes, as well as relative economic underdevelopment, diminish the attractiveness for medical personnel. This leads to a concentration of quality medical personnel and facilities in the southeastern provinces.

In addition, medical facilities in Shanghai are all equipped with baby-care rooms, which facilitate care for mothers and infants and breastfeeding. Medical insurance in Beijing covers several therapeutic assisted reproductive technology programs, providing more options for patients in need of assisted reproduction. Cities with a high density of maternal and child health care facilities are more amenable to the establishment of fertility-friendly hospitals.

Characteristics and advantages

Currently, the conceptual framework for and inherent meaning of "fertility-friendly hospitals" remain ambiguous, and a standardized definition is lacking. However, fertility-friendly hospitals should possess the following characteristics compared to other medical facilities. First, health care facilities must provide comprehensive services that cater to populations across various life stages, encompassing family planning, gestation, parturition, postnatal care, and pediatric health care. Secondly, associated disciplines, including obstetrics, gynecology, pediatrics, and neonatology, should have a high level of expertise. Third, these facilities should have superior material resources, characterized by state-of-the-art medical equipment and facilities that prioritize patient comfort, such as humanized wards, labor rooms, and mother-infant units. Fourth, patient education campaigns should emphasize information promoting fertility, ensure that the information, its dissemination, and effectiveness align with patient-centric values, uphold patient rights, and actively involve patients in decision-making processes.

In comparison to conventional medical facilities, hospitals that are attuned to fertility concerns tend to adhere more to evidence-based practices that encourage lactation and intimate mother-infant bonding. Empirical research has indicated that the prevalence of exclusive breastfeeding is notably higher in regions where a substantial number of hospitals and maternal health care facilities advocate for fertility-friendly services (*12*). This correlation contributes significantly to the improvement of neonatal health outcomes. The creation of fertility-friendly hospitals is beneficial in preventing rapid population aging, slowing the decline in fertility rates, contributing to a balanced population composition, and promoting balanced population development over the long term. By providing more supportive medical care, these hospitals help parents balance child-rearing and employment, reducing the impact of childbirth on women's career development (*13*).

Conclusion and suggestions

First, the effective advancement of fertility-friendly hospitals within China's health care landscape requires the establishment of unambiguous standards and characteristics for such facilities. This clarity

will facilitate superior practical implementation and adherence. Fertility-friendly hospitals should possess the capability to cater to individuals across a continuum of reproductive stages, including but not limited to family planning, antenatal, intrapartum, postpartum, and pediatric care. These defining features and the scope of services need to be meticulously delineated, thereby empowering health care facilities to deliver all-encompassing support for fertility and childbearing.

Second, given the uneven distribution of medical resources in China, medical personnel need to be allocated more rationally to ensure that fertility-friendly hospitals can better serve the population.

Third, the concept of fertility-friendliness should be integrated into traditional culture. Modern scientific practices need to be balanced with traditional cultural practices, merging modern medicine with traditional culture to facilitate the passing down of culture.

Fourth, current investment in the creation of fertility-friendly hospitals in China is limited; thus, an increase in resources is imperative to achieve significant results.

In addition, the current gender inequality in the household division of labor can restrict women's career development to some extent, affecting their desire to have children. If women's rights to career development can be safeguarded during childbearing and fathers are encouraged to actively participate in childcare, a social atmosphere of gender equality, respect for fertility, and emphasis on family can be created through culture and initiatives. These efforts can also provide a favorable social environment for the creation of fertility-friendly hospitals.

Funding: This study was supported by the 2023 Science and Technology Innovation Program of Shanghai Jiao Tong University School of Medicine (Humanities and Social Sciences) (grant number WK2316), the 2023 Youth Project of the Shanghai Hospital Association (grant number Q2023060), the 2023 Management Research Project of the Institute of Hospital Development Strategy, China Hospital Development Institute, Shanghai Jiao Tong University (grant number HDSI-2023-B-04).

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

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Received March 5, 2024; Revised April 2, 2024; Accepted April 18, 2024.

Released online in J-STAGE as advance publication April 21, 2024.

**Address correspondence to*:
Fei Ma, Outpatient and Emergency Department, Xinhua Hospital Affiliated with the Shanghai Jiao Tong University School of Medicine, 1665 Kong Jiang Road, Shanghai, China 200092.
E-mail: mafei@xinhuamed.com.cn

Global Health & Medicine. 2024; 6(3):222-224.

DOI: 10.35772/ghm.2023.01105

Rescue of outflow block of the remnant left liver after extended right hemihepatectomy for resection of a tumor in the caudate lobe

Shohei Kawaguchi[1], Shiro Onozawa[2], Hirokazu Momose[1], Ryota Matsuki[1], Masaharu Kogure[1], Yutaka Suzuki[1], Yoshihiro Sakamoto[1,*]

[1] Department of Hepato-Biliary-Pancreatic Surgery, Kyorin University Hospital, Tokyo, Japan;
[2] Department of Radiology, Kyorin University Hospital, Tokyo, Japan.

Abstract: Outflow block of the liver is a life-threatening event after living donor liver transplantation. Herein, we rescued a patient suffering from the outflow block of the remnant left hemiliver caused by bending of the left hepatic vein (LHV) after right hemihepatectomy plus caudate lobectomy combined with resection of the middle hepatic vein (MHV). A metastatic tumor sized 6 cm in the caudate lobe of the liver involving the root of the MHV was found in a 50's year old patient after resection of a right breast cancer eight years ago. Right hemihepatectomy and caudate lobectomy combined with resection of the MHV was performed using a two-stage hepatectomy (partial TIPE ALPPS). On day 1, the total bilirubin value increased to 4.5 mg/dL, and a dynamic computed tomography (CT) scan showed the bent LHV. On the diagnosis of outflow block of the left liver, a self-expandable metallic stent was placed in the LHV using an interventional approach, and the pressure in the LHV decreased from 27 cmH_2O to 12 cmH_2O. The bilirubin value decreased to 1.2 mg/dL on day 3. Outflow block of the LHV can happen after extended right hemihepatectomy with resection of the MHV. Early diagnosis and interventional stenting treatment can rescue the patient from congestive liver failure.

***Keywords*:** ALPPS, interventional stenting, left hepatic vein, liver failure, outflow block

Introduction

It is technically demanding to resect a metastatic tumor involving the major hepatic veins located in the caudate lobe of the liver. Extended hepatectomy with/without venous reconstruction using venous grafts has been performed occasionally (*1,2*), however there has been no report on the treatment for outflow block of the remnant liver caused by bending of the remnant major hepatic vein after major hepatectomy.

Outflow block of the liver is a serious problem unique to living donor liver transplantation (LDLT) seldomly found in orthotopic liver transplantation, which can be found in 6.5–7.1% after LDLT using left liver graft (*3-5*). Venous congestion of the transplanted graft can result in congestive liver failure. Thus, it is mandatory to make enough orifice of the major hepatic veins using venous grafts during outflow reconstruction of the right/left hemiliver graft (*6,7*).

Herein, we report on the interventional treatment in a patient suffering from outflow block of the left hepatic vein (LHV) after right hemihepatectomy plus caudate lobectomy combined with resection of the middle hepatic vein (MHV).

Patient & Surgical technique

The patient was a 60's year-old woman who underwent partial mastectomy and radiotherapy for a Stage I right breast cancer nine years ago. A metastatic hepatic tumor in the caudate lobe of the liver and thoracic nodal metastases were found four years after surgery. She received local radiotherapy and chemotherapy for three years. The response was stable disease for nodal metastases, however the hepatic tumor increased in size. Contrast-enhanced computed tomography (CT) showed a 60 × 50 mm low attenuation tumor in the caudate lobe of the liver. The tumors involved the three major hepatic veins, inferior vena cava (IVC) and the hepatic hilum (Figure 1A). Suppose that extended right hemihepatectomy was conducted, the future liver remnant volume (FLRV) was estimated as 27%. Indocyanine green retention (ICG) rate was 4.4%, and ICG-Krem was 0.056, which suggested marginal safety of upfront extended right hemihepatectomy. Thus, preoperative right portal vein embolization (PVE) to increase the remnant left hemiliver was necessary. However, the left portal vein appeared stenotic and compressed by the tumor (Figure 1B) and there was

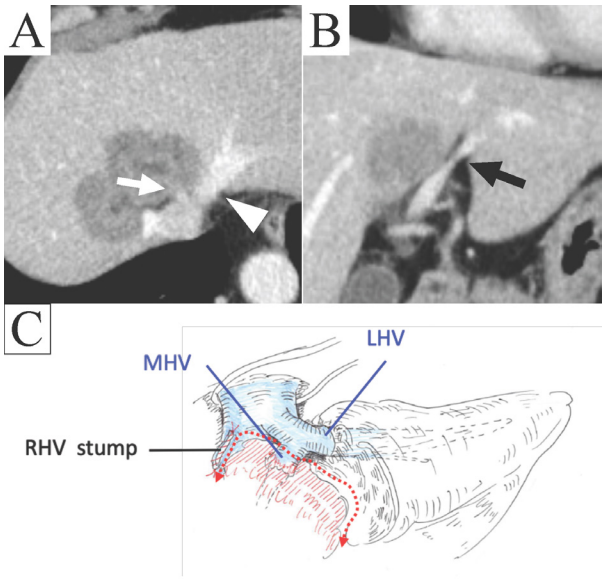

Figure 1. (A) Dynamic CT scan images of the liver tumor in the caudate lobe before surgery. The tumor involved roots of the three major hepatic veins. Middle hepatic vein (white arrow), left hepatic vein (white arrow head). **(B) The left portal vein appeared stenotic compressed by the tumor (black arrow). (C) The MHV was divided while preserving the LHV circumferentially.** CT, computed tomography; LHV, left hepatic vein; MHV, middle hepatic vein.

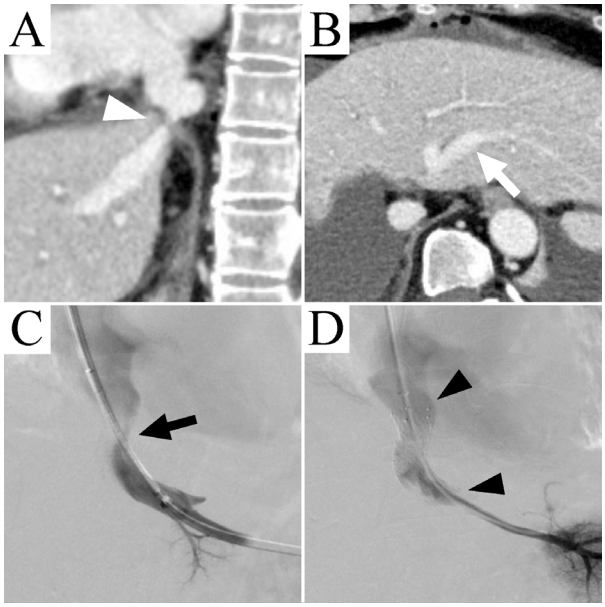

Figure 2. (A) Contrast-enhanced CT the day after 2nd stage hepatectomy. The bending of remnant LHV (white arrow head). **(B) The LHV trunk is patent (white arrow). (C) Interventional treatment of the stenosis of the remnant left hepatic vein through the right jugular vein.** The black arrow shows the stenotic point on the root of the left hepatic vein. **(D) A self-expandable stent was bridged between the left hepatic vein and the IVC.** The black arrow heads indicate the both ends of the stent. CT, computed tomography; LHV, left hepatic vein; MHV, middle hepatic vein.

a considerable possibility that right PVE remarkably increases the portal pressure.

Therefore, we introduced two-stage hepatectomy named partial TIPE ALPPS (*8,9*), that is, associating liver partial partition associated with trans-ileocecal portal vein embolization for staged hepatectomy. Briefly, at the 1st stage, exploration of the resectability of the tumor focusing on the left hilar plate, partial partition of the liver along the Rex-Cantlie's line preserving the MHV, and trans-ileocecal right PVE using digital subtraction image were performed. We confirmed that the tumor could be dissected from the hepatic hilum and IVC or major hepatic veins safely. The portal pressure increased from 10 cmH_2O to 15 cmH_2O before and after PVE suggestingenough patency of the left portal vein. Three weeks after the 1st stage, the FLRV was 36.2% (576 mL) and ICG-Krem was 0.057. Right hemihepatectomy plus total caudate lobectomy combined with resection of the MHV was performed. Fortunately, the tumor was dissected from the hepatic hilum and IVC completely. The confluent of LHV and MHV was strongly compressed by the tumor and the LHV was stretched longitudinally. The MHV was divided while preserving the LHV circumferentially (Figure 1C). Immediately after hepatectomy, the remnant left hemiliver transiently palpated elastic hard suggesting mild congestion. Adequate antegrade venous flow of the LHV was repeatedly confirmed using Doppler ultrasonography before closure of the abdomen. The falciform ligament was shrunk after two stage hepatectomies, and thus was not fixed on the midline incision.

On day 1, the total bilirubin value increased to 4.5 mg/dL. Dynamic CT scan showed the bending of the remnant LHV (Figure 2A) and the enlarged remnant left hemiliver (800 mL) deviated to the right side (Figure 2B). On the diagnosis of outflow block of the remnant left liver, an emergent interventional stenting was performed *via* the right jugular vein (Figure 2C). A self-expandable stent (Epic, Boston Scientific, Marlborough, MA, USA) with a size of 12 mm diameter and 6 cm length was deployed between the LHV and IVC (Figure 2D). The venous pressure in the LHV decreased from 27 cmH_2O to 12 cmH_2O. The bilirubin value decreased to 1.2 mg/dL on day 3 and the patient was discharged on day 15.

Cause of outflow block of the left hepatic vein and it's solution after right hemihepatectomy

Venous outflow block of the remnant liver happened after right hemihepatectomy plus total caudate lobectomy with resection of the MHV. The caudate large tumor stretched the confluent of the LHV and MHV, in other words, the stretched LHV was supported by the tumor with the MHV. Thus, the LHV lost support by the tumor and MHV after surgical resection and was bent. This rapidly caused the congestion of the remnant

left liver leading to congestive liver failure. Emergent placement of the metallic stent in the LHV decreased the venous pressure by 15 mmH_2O, and thereby prevented irreversible liver failure.

Hepatic venous outflow block is one of the serious complications leading to graft dysfunction after LDLT. The size, length and angle of the hepatic venous anastomosis and the graft position in the abdomen will affect the occurrence of outflow block (*4,5*). Outflow block can be found more often in the left liver graft rather than right liver graft, because the smaller left graft regenerates toward the right and dorsal side, and the topological position of the LHV and/or MHV will be changed rapidly.

In the present case, the size of the LHV was enough, but the stretched LHV losing support by the tumor and MHV was bent, and mild transient congestion of the remnant liver was found intraoperatively. We did not fix the falciform ligament to the midline incision before closure of the abdomen. This may cause bending of the LHV, but simultaneously this may let the remarkable enlargement of the remnant left liver dislodged to the right side, avoiding occlusion of the LHV.

A modified two-stage hepatectomy, named partial TIPE ALPPS was used to obtain enough FLRV before hepatectomy. In the present case, two stage hepatectomy was used *i*) to increase the FRLV effectively, and *ii*) to explore the resectability of the hepatic tumor against the left hepatic duct and IVC or major hepatic veins. Originally ALPPS was introduced in Europe and South America to obtain rapid growth of the FLRV for resection of advanced liver cancers, but was associated with high morbidity and mortality rates up to 9% even in patients with liver metastasis (*10*). Among several modified ALPPS procedures, partial ALPPS will be associated with better hypertrophy of the FLR and with low mortality rates (*11*). In our experience, we have no severe morbidity caused by partial TIPE ALPPS (*8,9*).

In conclusion, we experienced outflow block of the remnant left hemiliver caused by bending of the sole left hepatic vein after extended right hemihepatectomy. It is important to suspect venous outflow block when hyperbilirubinemia and congestion of the remnant liver were found after extensive hemihepatectomy. Prompt interventional stenting will be very effective to restore venous blood flow.

Funding: None.

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

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Received October 7, 2023; Revised February 8, 2024; Accepted February 29, 2024.

Released online in J-STAGE as advance publication March 27, 2024.

**Address correspondence to*:
Yoshihiro Sakamoto, Department of Hepato-Biliary-Pancreatic Surgery, Kyorin University Hospital, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan.
E-mail: yosakamo@ks.kyorin-u.ac.jp

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Comments			
Correspondence			
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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).

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(*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

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Global Health & Medicine

Volume 1, Number 1
October, 2019

www.globalhealthmedicine.com