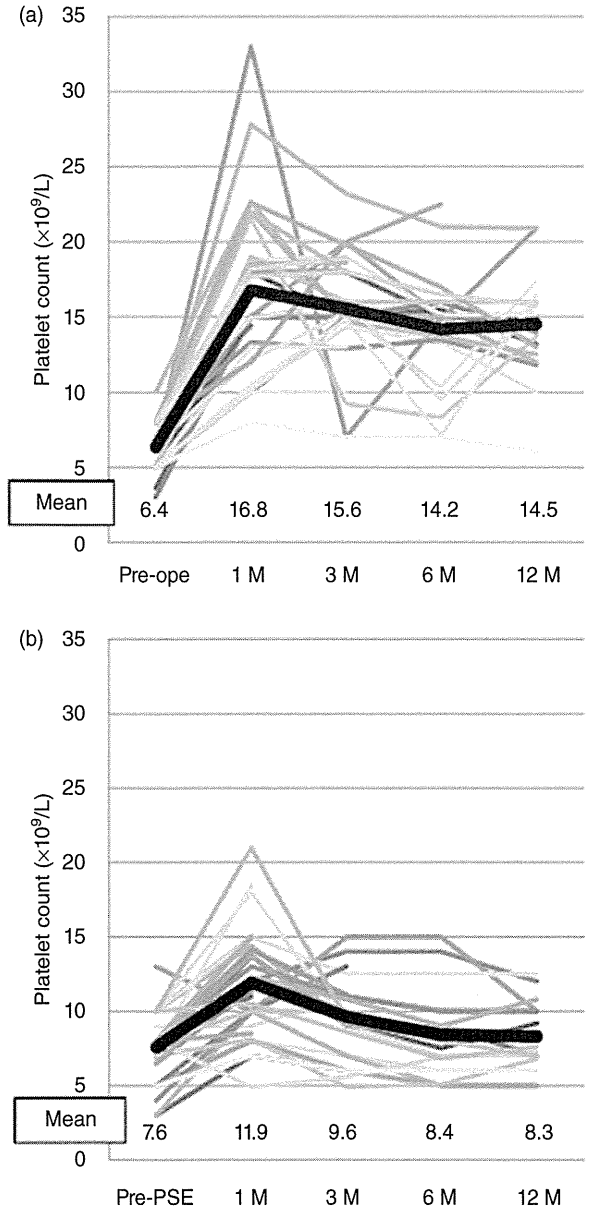

Figure 1 Platelet count transition of each institute following splenectomy/partial splenic embolization (PSE); average platelet count number of institutes. The bold line represents the transition of the mean platelet counts of each institute. (a) Splenectomy cases. (b) PSE cases.

3 – 6 months following splenectomy in the majority of cases (Table 2).

Complications following splenectomy/PSE

The splenectomy-associated complications experienced in each institute included portal thrombosis (28 of 63 institutes), postoperative infectious diseases (11 of 63 institutes) and ascites (12 of 62 institutes). However, the incidence of these complications varied depending on the institute.

In 64 institutes, fever ($n = 28$), thrombosis ($n = 22$), abscess ($n = 4$) and ascites ($n = 12$) were reported as frequent complications after PSE. However, the incidence of these complications also varied depending on the institute.

From 2005 to 2010, patient deaths were observed in seven of 788 (0.89%) cases of splenectomy, and in four of 474 (0.84%) cases of PSE. In nine of the 11 death cases, there appeared to be causal relationship between death and splenectomy as well as PSE (a causal relationship was indicated to exist by five of seven institutes for splenectomy and four of four institutes for PSE).

The age at the time of death ranged 46–70 years, with many patients older than 60 years. The sex included six male cases and five female cases, and there were two cases of chronic hepatitis and nine cases of liver cirrhosis (Child–Pugh classification grade A, two cases; B, six cases; and unknown, one case). The cirrhotic patients that died tended to have higher Child–Pugh scores and poor residual hepatic function. Pneumococcal vaccine inoculation was only performed in one splenectomy patient, and the other 10 patients were not inoculated. The cause of death was related to infectious diseases in nine cases (there was one patient with an apparent pneumococcal infection who was not inoculated with a pneumococcal vaccine). In most cases, death occurred within 3 months after treatment (splenectomy or PSE), although it also occurred over 3 months after treatment. Three patients died during IFN treatment (two cases after splenectomy, one case after PSE). Two patients died within 3 months after IFN treatment (two cases after splenectomy) (Table 3).

SVR rate of cases in which IFN treatment was performed following splenectomy or PSE

Among patients with low platelet count, IFN treatment was introduced in 92% (236/257) of the cases in which

Table 2 Period from splenectomy/PSE to initiation of IFN treatment

	Splenectomy ($n = 64$)	PSE ($n = 56$)
Within 1 month	6 (9%)	23 (42%)
>1 to 3 months	26 (41%)	23 (42%)
>3 to 6 months	17 (27%)	6 (10%)
>6 to 12 months	8 (12%)	3 (5%)
>12 months	7 (11%)	1 (1%)

IFN, interferon; PSE, partial splenic embolization.

Table 3 Period from splenectomy/PSE to death

	Splenectomy (7 cases of death)	PSE (4 cases of death)
Within 3 months	3 §Postoperative bleeding (hemophilia) §Pancreatic fistula, local infection §Intra-abdominal abscess (MRSA)	3 §Thrombocytopenia, cerebral hemorrhage §Pneumonia, ARDS, sepsis (MRSA) §Peritonitis
Within 6 months	0	1 †Spondylodiscitis, sepsis
Within 1 year	2 †SAH, bacteremia (MRSA) ‡Sepsis	0
Within 2 years	1 ‡Liver failure, suspect of SBP	0
Over 2 years	1 †Pneumococcal infection	0

†Death occurred during IFN treatment.
‡Death occurred within 3 months after IFN treatment.
§Death except † and ‡.
ARDS, acute respiratory distress syndrome; MRSA, methicillin-resistant *Staphylococcus aureus*; PSE, partial splenic embolization; SAH, subarachnoid hemorrhage; SBP, spontaneous bacterial peritonitis.

splenectomy was performed for IFN, 94% (295/314) of the cases in which PSE was performed for IFN, and 84% (241/285) of cases in which such pretreatment (splenectomy or PSE) was not performed before the introduction of IFN. Discontinuation of IFN occurred in 22% of cases of splenectomy, 28% of cases of PSE and 33% of those without pretreatment. Due to the pretreatment, the IFN introduction rates were increased ($P < 0.001$) and discontinuation rate declined ($P = 0.02$).

The pretreatment platelet count was $64 \times 10^9 \pm 17 \times 10^9$ platelets/L in splenectomy cases and $76 \times 10^9 \pm 21 \times 10^9$ platelets/L in PSE cases, while that of cases without pretreatment was $85 \times 10^9 \pm 16 \times 10^9$ platelets/L. In patients with a platelet count of 80×10^9 platelets/L or more, the majority of IFN treatments were without pretreatment to increase the platelet count.

The tabulation of the IFN treatment effects of cases in each institute is shown in Table 4. The SVR rate of cases of HCV genotype 1b and high viral load was 42 of 228 (22%) for the PSE group and 63 of 228 (28%) for the splenectomy group, with an odds ratio of 0.78 ($P = 0.19$). The SVR rate of so-called "others" (patients other than those with genotype 1b and high viral load) was 62 of 110 (56%) for the PSE group and 84 of 119 (71%) for the splenectomy group, with an odds ratio of 0.54 ($P = 0.025$). Additionally, in the "others" group, the SVR rate following IFN treatment was higher in patients who underwent splenectomy compared to that of patients who underwent PSE.

DISCUSSION

THE PRESENT STUDY was conducted to clarify the current conditions of splenectomy/PSE performed for the purpose of IFN treatment. This was the first national questionnaire conducted in Japan, and no similar studies have been reported previously. The results of these questionnaires revealed that the lower limit of the platelet count achieved prior to IFN administration varied widely depending on the institute in

Table 4 SVR rate of IFN treatment following splenectomy/PSE

	Splenectomy	PSE	*P* (odds ratio)
1b-high	28% (63/228)	22% (42/190)	0.19 (0.74)
Others	71% (84/119)	56% (62/110)	0.025 (0.54)

A difference in SVR rate was observed between splenectomy and PSE groups. In patients with hepatitis C virus genotype 1b and a high viral load, there was no significant difference in the low SVR rate. The SVR rate was high in cases other than those of a 1b genotype/high viral load, with splenectomy having a significantly higher SVR rate compared to PSE.
IFN, interferon; PSE, partial splenic embolization; SVR, sustained virological response.

Japan. Currently, for pegylated (PEG) IFN-α-2a/RBV treatment of liver cirrhosis, Japanese insurance considers a platelet count of 75×10^9 platelets/L or more as the standard count for treatment initiation and less than 50×10^9 platelets/L as that for discontinuation. However, it is now clear that half of the specialized institutes surveyed were initiating IFN therapy even in patients with platelet counts below the recommended value, and 9% of institutes were administrating IFN even in patients with platelet counts below the standard discontinuation value. Moreover, there was disproportionate selection and application of splenectomy and/or PSE, perhaps because each institute tended to select its experienced method. Therefore, in order to obtain consensus in the future, it is necessary to investigate the actual situation of splenectomy/PSE treatment in HCV positive patients with a low platelet count through the collection of clinical data.

Beneficial information regarding the effects of splenectomy and/or PSE on IFN treatment for the patients was also obtained from this questionnaire. The platelet counts increased after splenectomy and/or PSE, thus resulting in the improvement of adherence to IFN treatment. However, an increased SVR rate was not prominent in patients with HCV genotype 1b and a high viral load. It was presumed that if the viral factor shows IFN-resistant characteristics and liver cirrhosis exists as an intractable factor on the patient side, only a small number of patients will achieve a SVR with PEG IFN/RBV treatment, despite increased platelet counts and IFN adherence following splenectomy and/or PSE. However, in the case of "others", a relatively high SVR rate was observed (Table 4). Interestingly, the SVR rate of the "others" splenectomy group was significantly higher than that of the "others" PSE group, despite the pretreatment platelet count being lower in the splenectomy group than that of the PSE group. If the platelet count is less than 80×10^9 platelets/L in cases of "others," anti-hypersplenism treatment should be performed to increase the platelet count, and we suggest that splenectomy should be selected because of its strong effect on the increase of the platelet count.

Many complications regarding patients' safety were observed in both splenectomy and PSE groups, and it should be noted that slightly less than 1% cases resulted in death. Most patients had liver cirrhosis. These patients typically have several medical problems that can become severe if they are not receiving anti-HCV therapy, including decompensated cirrhosis and/or the development of HCC. However, the high mortality rate reported in the present study should not be overlooked. We recommend that the application of splenectomy/PSE prior to IFN treatment should be chosen with careful consideration.

At present, splenectomy/PSE is also mentioned in the Guidelines for IFN Treatments in Liver Cirrhosis C in Japan as treatments for patients with low platelet counts, although the risk of death due to splenectomy/PSE for the purpose of IFN treatment has not been studied previously. Death was related to infections in many cases, but the rate of pneumococcal vaccine inoculation was low in cases of death. According to the questionnaire results, within institutes administrating pneumococcal vaccines when performing splenectomy, the vaccination rate was 80% or more in the department of internal medicine and 60% or more in the surgical department; however, this rate was only approximately 20% for PSE. The pneumococcal vaccine is inoculated at a high rate for splenectomy based on the recommendations from the insurance guidelines[29] and infection prevention guidelines.[30–32] In contrast, there is no evidence indicating the usefulness of pneumococcal vaccine inoculation when performing PSE, in which splenic function is preserved. Therefore, this vaccine was not given to patients undergoing PSE in many cases. However, considering the fact that most causes of death were related to infections, pneumococcal vaccine inoculation should also be necessary when carrying out PSE. Moreover, vaccinations against bacteria other than *Streptococcus pneumoniae* such as *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis*, which mainly exhibit immune reactions in the spleen, may be important to administrate before splenectomy and/or PSE.[33–36]

Deaths were primarily observed in Child–Pugh B or C cirrhotic patients and those aged above 60 years. Therefore, splenectomy/PSE must be applied with care in patients with poor residual hepatic function and elderly patients.[37,38]

As a result of this questionnaire, we determined that adherence to IFN treatment was increased by splenectomy and/or PSE; however, in patients with HCV genotype 1b and a high viral load, the rate of SVR was not improved. Therefore, splenectomy and/or PSE must be limited to the cases in which IFN is likely to be effective. In addition, it is essential to predict the sensitivity of IFN treatment by evaluating the IFN sensitivity-determining region of HCV, core domain amino acid 70 of HCV and interleukin-28B, as well as hepatic functional reserves and age before splenectomy and/or PSE. In the future, treatment by various oral therapeutic agents (direct antiviral agents) may be selected without administrating IFN for patients with low platelet counts.[39,40]

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ANATOMIC VARIATIONS

A rare congenital extrahepatic portosystemic shunt affecting the inferior mesenteric vein, inferior vena cava, and left ovarian vein

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Abstract
Purpose To observe a case of congenital extrahepatic portosystemic shunt and discuss it from the embryological and clinical viewpoints.
Methods An 85-year-old female cadaver was employed for a dissection course at Aichi Medical University in 2009.
Results There was no evidence of liver cirrhosis macroscopically or microscopically. A portosystemic shunt was observed that involved communication between the inferior mesenteric vein, inferior vena cava (IVC), and left ovarian vein by a single Y-shaped shunt vessel.
Conclusions To the best of our knowledge, this is the first reported case of the above-mentioned three veins being connected by a single Y-shaped shunt vessel. Considering the other venous diameters, the shunt appeared to flow into the splenic vein and IVC. It cannot be denied that this shunt may have led to hepatic encephalopathy, although the shunt effect may have been minimal. Embryological development of IVC appears to occur close to the plexus of anastomosing vitelline veins, forming the portal vein.

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Introduction

Communications between the portal vein (PV) and vena cava systems outside the liver are generally known as extrahepatic portosystemic shunts (EPSs) and commonly occur at the plexuses of the esophageal, rectal, and paraumbilical veins [5]. Although EPSs are associated with portal hypertension, some occasionally occur without any marked histological changes in the liver as congenital extrahepatic portosystemic shunts (CEPSs) [9]. Congenital portosystemic shunts are associated with complications such as encephalopathy, benign and malignant liver tumors, hepatopulmonary syndrome, and neonatal cholestasis [2]. Here we report a case of CEPS that involved the inferior mesenteric vein (IMV), inferior vena cava (IVC), and left ovarian vein (LOV). To the best of our knowledge, this is the first reported example of these three veins being connected by a single Y-shaped shunt vessel. The present study was conducted in accordance with the provisions of the Declaration of Helsinki, 1995 (as revised in Edinburgh, 2000).

Case report

An 85-year-old female cadaver was employed for a dissection course at Aichi Medical University in 2009. There was no macroscopic evidence of abdominal surgery, either on the surface or in the abdominal cavity. We observed and recorded the shunt vessel, paying close attention to its

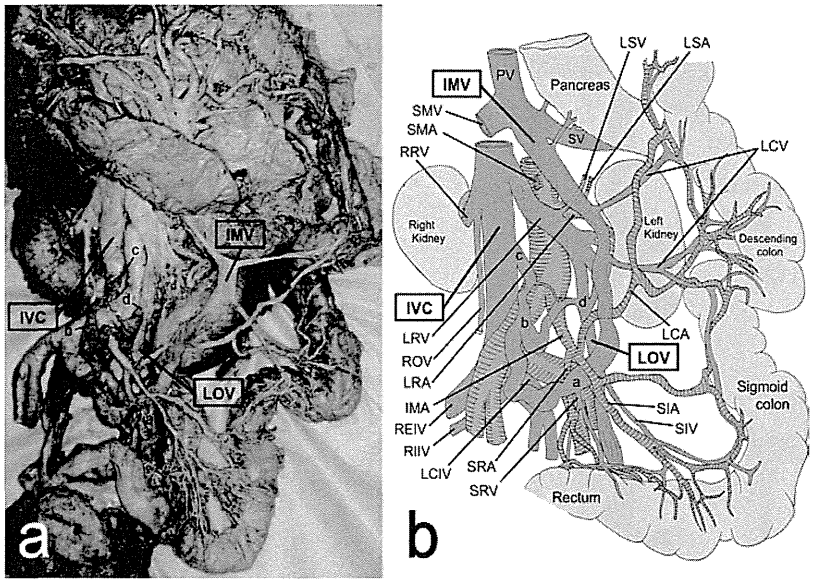

Fig. 1 Photograph and schema of this case The letters *a–e* in panel **b** indicate the points at which the external diameter was measured. *IMA* inferior mesenteric artery, *IMV* inferior mesenteric vein, *IVC* inferior vena cava, *LCA* left colic artery, *LCV* left colic vein, *LCIV* left common iliac vein, *LOV* left ovarian vein, *LRA* left renal artery, *LRV* left renal vein, *LSA* left suprarenal artery, *LSV* left suprarenal vein, *PV* portal vein, *RCIV* right common iliac vein, *REIV* right external iliac vein, *RIIV* right internal iliac vein, *ROV* right ovarian vein, *RRV* right renal vein, *SIA* sigmoid artery, *SIV* sigmoid vein, *SV* splenic vein, *SMA* superior mesenteric artery, *SMV* superior mesenteric vein, *SRA* superior rectal artery, *SRV* superior rectal vein

relationships with IMV, IVC, LOV, and their branches. The portosystemic shunt (PS) involved communication between IMV, IVC, and LOV (Fig. 1a, b) by a single Y-shaped shunt vessel. After branching of the superior rectal vein (SRV) from IMV (Fig. 1: point a), the shunt divided (Fig. 1: point b), one branch connecting with IVC (Fig. 1: point c) and the other with LOV (Fig. 1: point d). The external diameters at points a, c, and d were 11.0, 6.0, and 8.0 mm, respectively, whereas those of the PV, superior mesenteric vein (SMV), IMV, and splenic vein (SV) were 10.6, 14.3, 9.7, and 9.0 mm at their widest portions. The length of the shunt between points b and c was 14.5 mm and that between points a and d was 11.3 mm. The shunt crossed the ventral aspect of the left colic artery (LCA), dorsal aspect of the sigmoid artery (SIA), and ventral aspect of the superior rectal artery (SRA) and abdominal aorta. The right and left renal veins ran along the ventral aspect of the renal arteries (RAs). The right and left ovarian veins were varicose and flowed into the renal veins (RVs). A vessel communicating between LOV and the left renal vein (LRV) was found (Fig. 1a, b). The right common iliac vein was absent, and the right internal iliac vein flowed into the left common iliac vein. The surface of the liver was flat and macroscopically normal. There was no evidence of liver cirrhosis or primary biliary cirrhosis. The lobular connective tissue was not increased, and the sinusoids were not narrowed. The hepatic cell cords were normal, and no bile stasis was observed.

Discussion

A case of CEPS with communication between IMV, IVC, and LOV by a single Y-shaped shunt vessel is reported. IMV-systemic shunt is found in approximately 12.5 % cases of EPS. The drainage veins of 24 cases of IMV-systemic shunts have been reported as follows: direct shunt to IVC (Fig. 2a, 11 cases), to the left gonadal vein (LGV) (Fig. 2b, 7 cases), to the left internal iliac vein (LIIV) (Fig. 2c, 5 cases), and to the right gonadal vein (RGV) (Fig. 2d, 1 case) [5]. Because of their clinical and embryological interest, several classifications of PS have been devised. One of the earliest descriptions of PS was given by Abernethy in 1793, and the condition was classified into two types. Type 1 was an end-to-side shunt with congenital absence of the PV, and Type 2 was a side-to-side shunt between the portal and systemic veins [1]. Later, Morgan and Superina [7] subclassified Type 2 into Type 2a (congenital) and Type 2b (acquired). The diagnostic criteria for congenital PS can be summarized as a lack of any marked microscopic change in liver specimens, such as hepatitis, cirrhosis, or idiopathic portal hypertension, and no history of portal hypertension or abdominal surgery [9]. In the present case, we found no macroscopic evidence of abdominal surgery. The external diameter of PV was 10.6 mm, i.e., it was not enlarged in comparison with the normal external diameter of 10 mm. The microscopic findings of the liver

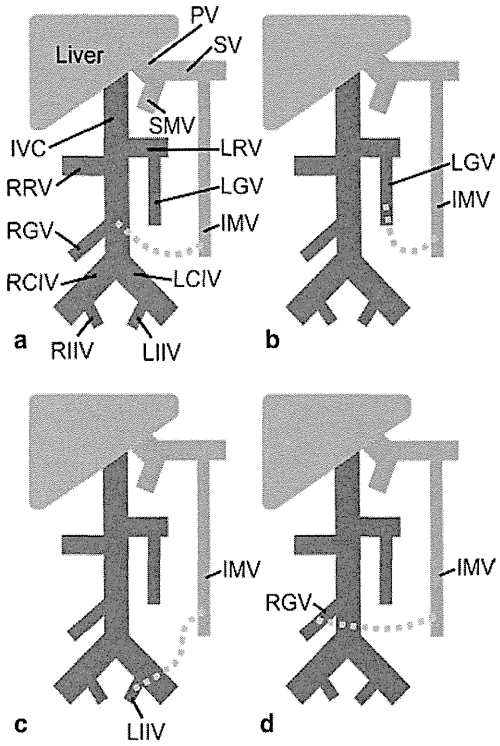

Fig. 2 The drainage veins of IMV-systemic shunts. **a** Direct shunt to IVC, **b** shunt to the LGV, **c** shunt to the LIIV, **d** shunt to the RGV. *LGV* Left gonadal vein, *LIIV* left internal iliac vein, *RGV* right gonadal vein

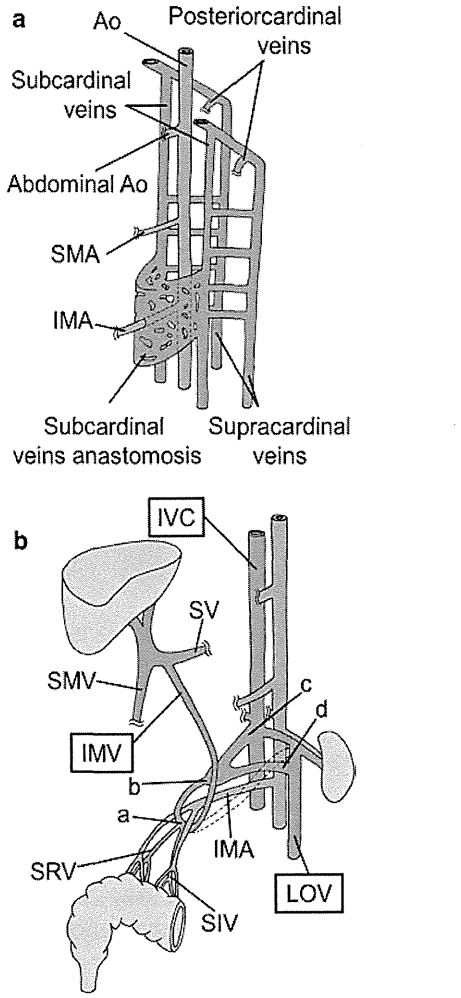

Fig. 3 The developmental origins and their interrelationships associated with the present case. The letters *a–d* in panel **b** indicate the points connecting with SRV (point *a*), IVC (point *c*) and LOV (point *d*); the shunt divided at point *b*. Aorta, Ao

also indicated that portal hypertension was unlikely to have occurred. These findings indicate that this case is most likely to be CEPS. The frequency of Type 2a is unclear, although in a previously reported series, congenital PS was found in only 1 of 145,000 infants [3]. In 51 congenital PS cases reported by Uchino et al. [13], the incidence of CEPS (17 cases; 33 %) was less than that of congenital intrahepatic PS (34 cases; 67 %). In addition, according to a review of 136 cases of CEPS by Kobayashi et al. [5], Type 2 occurred in 22 % (30) cases and CEPS involving IMV was found in only 8.8 % (12) cases. Only one case of CEPS connecting IVC and IMV without portal hypertension has been reported [8], but there has been no previously reported case of CEPS in which IMV drains directly into IVC.

From the viewpoint of clinical medicine, EPS is generally known to be a cause of hepatic encephalopathy, because PV flows directly into IVC and circulating toxins that normally undergo first-pass metabolism in the liver then affect the brain [10]. In the present case, considering the other venous diameters, the shunt appeared to flow into SV and IVC. Flow into the latter may have caused the left ovarian varicosis. It cannot be denied that this shunt may have led to hepatic encephalopathy, although the shunt effect may have been minimal.

Embryologically, the abdominal veins inferior to the renal veins are developed by the cardinal venous system and vitelline venous system. The cardinal venous system develops in the 3rd and 4th weeks of gestation and consists of paired posterior cardinal veins that are replaced by pairs of subcardinal and supracardinal veins (Fig. 3a). The right subcardinal vein forms a portion of IVC inferior to the kidneys. By the 7th and 8th weeks, the main part of the left subcardinal vein regresses, excluding of a portion associated with the left gonadal vein and bilateral anastomosis between bilateral subcardinal veins left as the left renal vein (Fig. 3b). Prominent left-to-right anastomoses between the vitelline veins caudal to the liver are remodeled to the distal end of PV through two veins: SV and IMV [4, 6]. In this case, the shunt vessel connected to IMV, IVC, and LOV, with IMV anastomosed to SV.

Considering that IMV is derived from the vitelline veins, and IVC and LOV are derived from the cardinal veins, the case suggests that vitelline venous system is once associated with the bilateral subcardinal veins anastomosis (Fig. 3b).

As mentioned above, EPSs from IMV are very rare [5], although in such cases, a shunt to IVC or LOV is relatively common [11]. In the present case, it is of interest that IVC directly communicated with IMV. Although PS is usually a single vein, Tanaka et al. [12] reported a case with two different shunt vessels: one from IMV to IVC and the other from IMV to LOV. These two shunt vessels were not connected. In the present case, a single Y-shaped shunt vessel was connected to IMV, IVC, and LOV. To the best of our knowledge, this is the first reported case of its kind to suggest that the venous plexus between the cardinal veins may be associated with the conformation of CEPSs. The subcardinal vein anastomosis is believed to intricately develop around the artery (Fig. 3a), but the details remain to be confirmed. Moreover, it is highly assumed that there had been communication between IMV and subcardinal veins anastomosis; otherwise the communication position is not clear (Fig. 3b). Although few reports have described the positional relationship of the arteries and veins associated with EPSs [4], the findings in the present case may help to resolve some hitherto unknown aspects of the development of abdominal veins.

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Conflict of interest The authors declare that they have no conflict of interest.

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Comparison of tutored group with tutorless group in problem-based mixed learning sessions: a randomized cross-matched study

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Abstract

Background: Problem-based learning (PBL) involves discussions among students who resolve loosely-structured problems to facilitate learning. In the PBL curriculum, faculty tutors are employed as facilitators for small groups of students. Because of lack of time and staff shortage, the effectiveness of tutorless PBL has been discussed as an alternate option.

Methods: Sessions in which tutored and tutorless PBL groups are mixed were presented by 1st-year medical students, who experienced both tutored and tutorless groups alternately in the two sessions of a year. To examine the effectiveness of tutored and tutorless PBL, written examination scores (WES) and self-contentment scores (SCS) were statistically analysed.

Results: WES averages did not significantly differ between the tutored and tutorless groups; however, a significantly greater variation was observed in WES in the tutorless group. SCS averages tended to be higher in the tutored PBL than in tutorless PBL groups.

Conclusions: Students in these tutorless PBL groups performed well in their written examinations, whereas those in the tutored PBL groups, achieved this and reported better self-contentment with their learning experience. Tutorless PBL sessions were considered to be comparable to tutored PBL sessions at least in the early stages.

Keywords: Problem-based learning, Tutorless group, Curriculum, Large class, Learning strategy

Background

In the mid-1960s, problem-based learning (PBL) was adopted as a new approach for medical education at McMaster University, Ontario, Canada. PBL has been described as 'a learning that results from the process of working towards understanding or resolution of a problem' [1]. PBL not only facilitates the acquisition of knowledge but also that of other generic desirable attributes such as effective communication skills, ability to work in a team (team work), problem-solving skills, self-directed learning ability, ability to share information, appreciate other points of view and identification of personal strengths and weaknesses [2]. Because many of these skills are related to the tutorial process and group dynamics [3], the tutors' expertise, characteristics and behaviour are believed to influence both the process perspective and learning outcomes [4,5].

In the approach adopted by the McMaster University medical school, a faculty tutor was present during all group activities to monitor, assess and provide immediate input i. e. each group was tutored [6]. Providing a facilitator for PBL can be a problem during times of faculty/staff shortage [6-16]. Therefore, many schools have tried other PBL formats in an attempt to reduce the demands on faculty/staff time and resources; examples of these formats include student-tutored PBL [17] and tutorless PBL [6]. In student-tutored PBL, one student studies the problem in advance and then takes on the role as the tutor of the group instead of the faculty tutor. In tutorless PBL, neither the student tutor nor the faculty tutor is present. There have been many reports suggesting that student-tutored PBL can be just as effective as faculty-tutored

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PBL with regard to learning outcomes of student-tutored PBL. These sessions can be conducted by senior students [17-19] or also by peer-level students from the same class [3,9,10]. Similarly, a meta-analysis by Leary et al. [20] indicated that student tutors were equally effective when compared with faculty tutors. However, there is limited information on learning outcomes of tutorless PBL [11,14,15].

The aim of this study was to examine the effectiveness of tutorless PBL by comparing learning outcomes between tutorless and tutored groups. Roberts et al. [11] and Kaliyadan et al. [14] reported their experiences with tutorless PBL and concluded that there were no significant differences in learning outcomes between tutored and tutorless PBL. However, in the abovementioned reports, several important differences such as group member characteristics, scenarios or learning materials that were present between the tutored and tutorless PBL conditions were observed. Nicholl and Lou [15] recently reported on tutorless PBL using a model for a large class facilitated by one instructor; they argued that students could achieve the required learning outcomes with tutorless PBL. Moreover, these reports do not only compare learning outcomes between tutored and tutorless PBL because there are many other factors influencing the study and results. To the best of our knowledge, this is the first randomised cross-matched study comparing tutored and tutorless PBL.

Methods

At Aichi Medical University, the PBL course comprises the following two units: PBL1 for first year medical students and PBL2 for third and-forth year medical students. The goal of PBL1 is introduction and early exposure of clinical medicine to students, and the role of PBL2 is to train students on the art of clinical problem solving. Between 2007 and 2008, as part of the curriculum development of the existing PBL1, we conducted a randomised cross-matched study on the learning outcomes involved in PBL1 (2007, N = 102; 2008, N = 100). The research design is shown in Figure 1. The study was performed in accordance with the provisions of the Declaration of Helsinki. The executive council of the Medical Education Center Aichi Medical University first reviewed the detail protocol, including the future plan of submission. After the review by this committee, the academic affairs department and

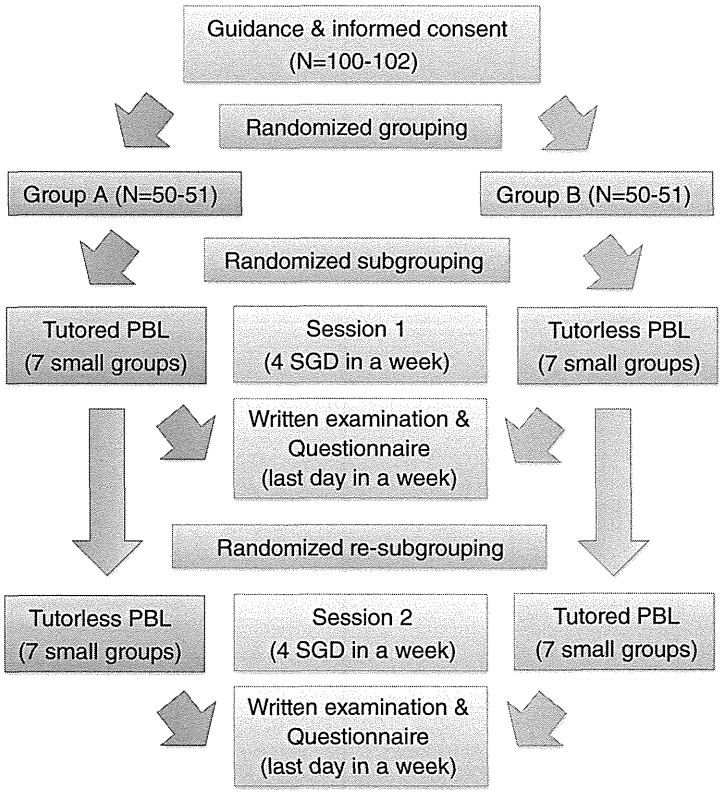

Figure 1 Chronological list of problem-based learning (PBL) undertaken by students in this study. Group A in the left row and Group B in the right row. In the middle row, sessions experienced by all students conducted in a large classroom are chronologically displayed.

the faculty council of our school approved this curriculum. The Institutional Review Board exempted the study from review.

These details were explained to all students prior to the start of PBL1, and they were advised that self-evaluation and a questionnaire were voluntary. Students were given the option of not participating in this research, but they all decided to participate. Students were randomly divided into two groups of equal numbers, Group A and Group B. Each group was randomly reorganised into seven small groups comprising seven or eight students for each session. All students attended two sessions in a year; every session covered a four day period (Figure 2). Small group discussions (SGDs) were conducted every day in each session about recurring scenario of chief complaints such as abdominal pain and cough, i.e. four SGDs per session. In group A, SGDs were tutored in the first session and tutorless in the second session. In group B, SGDs were tutorless in the first session and tutored in the second session. Each session was designed such that the schedule for lectures or laboratory practices did not coincide, except for a daily short lecture related to the scenario of each day. Both groups completed a daily report on every SGDs and noted details of any self-learning. On the last day, a written examination (full marks, 100 points) on the contents of each session was conducted. A questionnaire including a 5-tiered self-evaluation on self-contentment and other items shown in Table 1 was simultaneously distributed. An overall evaluation was conducted using a

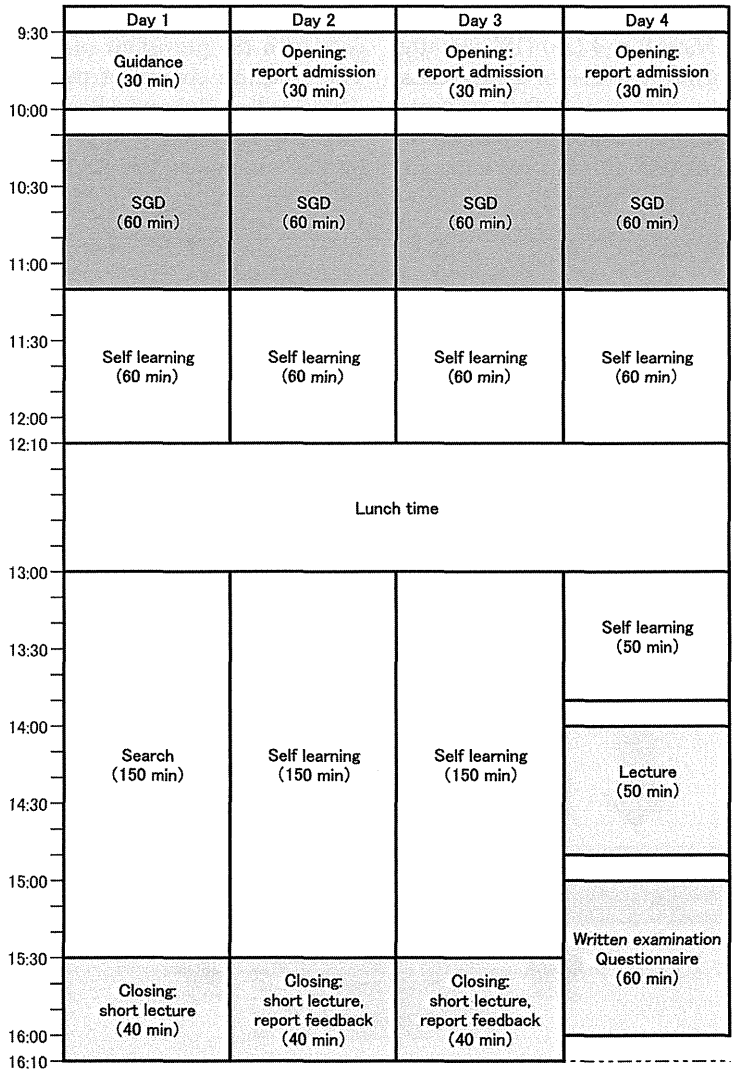

Figure 2 Timetable of each problem-based learning (PBL) session.

Table 1 Student results on the self-evaluation in each session

	2007									
	Session 1					*Session 2*				
	Group A: Tutored (n = 51)		**Group B: Tutorless (n = 50)**			**Group B: Tutored (n = 51)**		**Group A: Tutorless (n = 51)**		
	average	**SD**	**average**	**SD**	**p value**	**average**	**SD**	**average**	**SD**	**p value**
Self-directed learning	4.19	0.72	3.94	0.71	0.08	4.25	0.74	4.06	0.86	0.22
Activeness	4.13	0.77	4.06	0.71	0.60	4.35	0.72	4.20	0.83	0.31
Scientific basis	3.96	0.77	3.74	0.72	0.14	4.00	0.80	3.89	0.69	0.36
Group dynamics	4.31	0.79	3.88	0.96	0.02	4.57	0.61	4.27	0.72	0.03
Attentiveness	4.20	0.69	4.28	0.67	0.54	4.39	0.72	4.27	0.70	0.40
	2008									
	Session 1					*Session 2*				
	Group A: Tutored (n = 46)		**Group B: Tutorless (n = 45)**			**Group B: Tutored (n = 45)**		**Group A: Tutorless (n = 46)**		
	average	**SD**	**average**	**SD**	**p value**	**average**	**SD**	**average**	**SD**	**p value**
Self-directed Learning	4.41	0.75	4.42	0.70	0.96	4.51	0.59	4.24	0.66	0.037
Activeness	4.35	0.82	4.50	0.71	0.34	4.67	0.52	4.24	0.72	0.001
Scientific basis	4.20	0.78	4.34	0.66	0.33	4.44	0.62	4.14	0.70	0.027
Group dynamics	4.60	0.65	4.56	0.73	0.73	4.56	0.62	4.40	0.78	0.28
Attentiveness	4.50	0.72	4.58	0.57	0.55	4.60	0.50	4.40	0.67	0.19

combination of the percentage of attendance and written examination scores (WES). Daily reports, tutor evaluation, self-evaluation and answers to the questionnaire were not included in the summative evaluation.

The average value of WES and self-contentment scores (SCS) for each session was examined with the two-way analysis of variance (ANOVA) and uniformity of examinations was tested with the Tukey–Kramer's honesty significant difference (HSD) test. The validity of grouping during each year was examined using the unpaired t-test and Bartlett's test by comparing the total scores of Groups A and B. With regard to WES and self-evaluation results, the average values for the t-test and dispersion of the F-test were compared between the tutored and tutorless PBL groups. The value of $p<0.05$ (two-tailed) was considered statistically significant. Furthermore, all statistical analyses were conducted using JMP 8.0.1 (SAS institute Inc., Cary, North Carolina, USA) and Prism 6.0b (Graphpad software, Inc., San Diego, CA, USA).

Results

Validity of matching and reproducibility of the result

In 2007, the average ± standard deviation of WES in Groups A and B was 131.45 ± 22.32 and 135.86 ± 17.91, respectively. In 2008, WES in Groups A and B was 154.69 ± 29.85 and 135.86 ± 17.91, respectively. No significant difference was observed in the average value or standard deviation between both groups. Therefore, it was concluded that Groups A and B matched in each grade.

While comparing sessions, the average ± standard deviation of WES in 2007 was 64.98 ± 18.74 and 68.68 ± 14.91 for sessions 1 and 2, respectively. In 2008, WES was 76.80 ± 19.76 and 75.25 ± 19.26 for sessions 1 and 2, respectively. The two-way ANOVA recognised a significant effect associated with the year, but no significant effects according to sessions were observed. Furthermore, no significant difference was recognised in the Tukey–Kramer HSD test between sessions 1 and 2 in any year. The average score significantly differed between 2007 and 2008; however, because no difference was observed between the sessions in each year, results of sessions 1 and 2 for each year were considered to be reproducible. Therefore, it was decided that results for each year will be analysed by combining the results of sessions 1 and 2 in groups A and B, respectively, to form the tutored group and those of sessions 1 and 2 in groups B and A, respectively, to form the tutorless group.

Written examination scores

The average ± standard deviation of WES in 2007 was 67.83 ± 11.11 and 65.82 ± 13.42 in the tutored and tutorless groups, respectively. In 2008, WES was 77.85 ± 17.30 and

74.33 ± 21.28 in the tutored and tutorless groups, respectively (Figure 3).

In the tutorless groups, a tendency towards higher average scores during both years was observed, but this difference was not significant (2007, p = 0.25; 2008, p = 0.20). However, in 2008, variances tended to be significantly larger than the average score in the tutorless group (2007, p = 0.058; 2008, p = 0.039).

Self-contentment scores

In 2007, the average ± standard deviation for SCS was 4.08 ± 0.78 and 3.88 ± 0.88 in the tutored and tutorless groups, respectively. In 2008, SCS was 4.37 ± 0.76 and 4.29 ± 0.74 in the tutored and tutorless groups, respectively (Figure 3). In both years, the average score tended to be lower in the tutorless group but this was not significant (2007, p = 0.092; 2008, p = 0.42). A tendency in the variations from the average scores was inconsistent, and no significant differences were found (2007, p = 0.23; 2008, p = 0.75). No correlation was observed between WES and SCS in both years (2007, r = 0.023, p = 0.74; 2008, r = −0.021 p = 0.76).

Self-evaluation

Self-evaluation results, excluding SCS, for each session are shown in Table 1. In the tutored group of 2007, there was a tendency for high self-evaluation. In particular, self-evaluation of group dynamics were significantly different. However, inconsistent trends were recognised in 2008. In each student during both years, there was a tendency for high self-evaluation in the tutored PBL session but no significant differences were found. When the results of sessions 1 and 2 for both years were combined, no significant differences were found between the tutored and tutorless groups.

Discussion

In the present study, a mixed course comprising tutored and tutorless PBL was undertaken by first-year medical students, and the learning outcomes were analysed. The results indicate that students undertaking tutorless

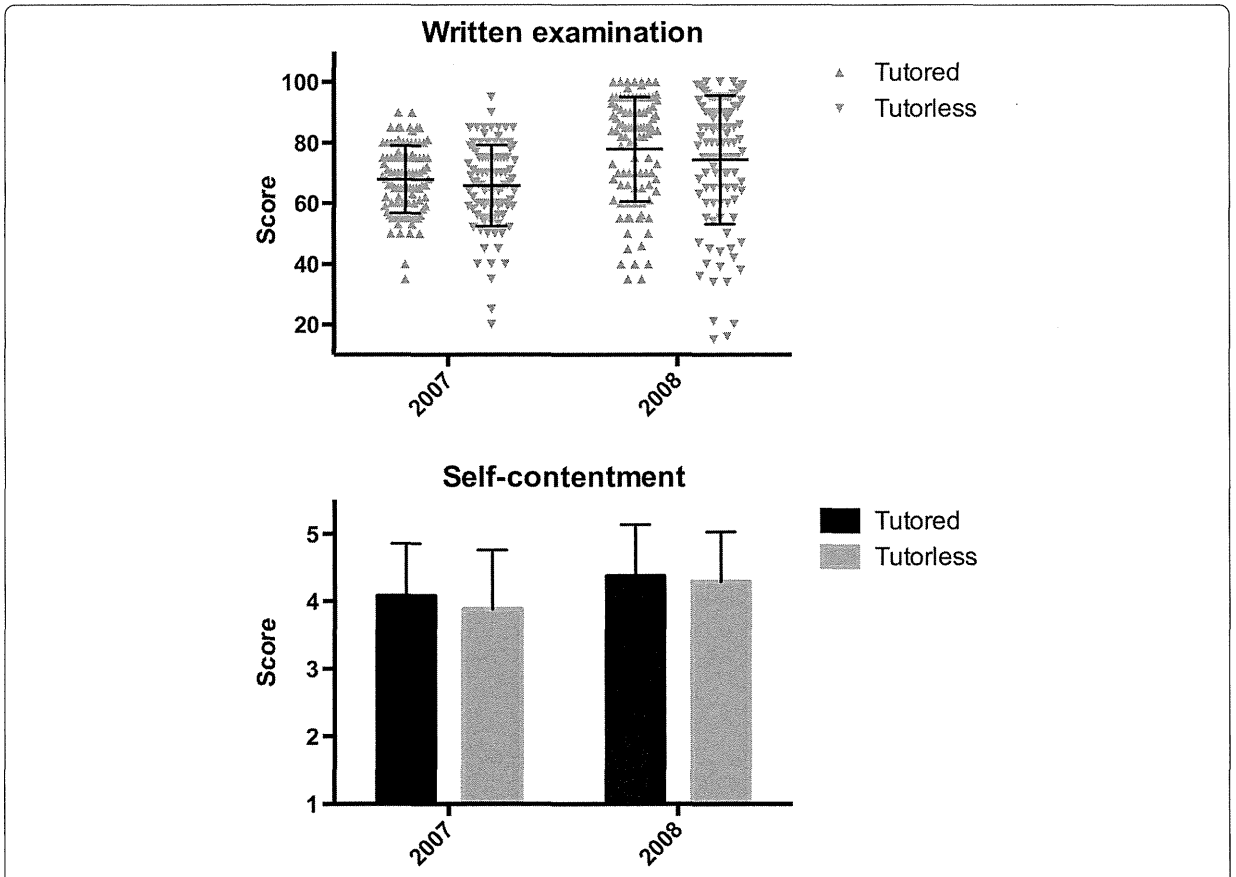

Figure 3 Students' performance on the written examination score and self-contentment score during each year. The error bars represent the standard deviations.

PBL were adequately prepared for written examinations, whereas tutored PBL prepares students for written examinations and also increases self-contentment with their learning experience.

Tutorless PBL is an efficient way to reduce demands on faculty time and resources [6,8,11,12,14,15]. However, tutorless PBL may give rise to several problems that may impede learning [21], and according to Duncan-Hewitt [8] these are as follows: (1) students' emotions can interfere with their willingness to participate and decrease their quality of learning, (2) misapprehensions and weak thinking, group and problem-solving skills can cause students to become engrossed in the problem-solving process, and the problem-solving skills can cause students to concentrate more on the problem-solving process and (3) there is no opportunity to directly examine students' abilities and skills, which can be systematically improved. Despite these problems, we did not provide any special intervention for students in the tutorless group; however, sufficient guidance was provided to all students in both the tutorless and tutored groups prior to PBL. In addition, following reports regarding SGD and self-learning, we provided formative evaluation and feedback every day. With regard to the fact that WES and SCS did not significantly differ between the tutorless and tutored groups, it appears that these traditional complementary methods may have affected the learning outcomes of the tutorless group.

In contrast, variances in WES scores were considerably greater in the tutorless than tutored groups. Moreover, the average SCS in the tutored group tended to be higher than that in the tutorless group. The daily report also appeared to show that the quality and quantity of SGD and self-learning varied widely in the tutorless group. These results imply that it is unavoidable that tutorless PBL may give rise to some students who do not learn well without a structured process, thereby receiving lower scores. Although the daily short lectures directed the students to study, Lee et al. [22] reported that these were not correlated with perceived self directed learning ability in their case-oriented problem-stimulated mixed PBL curriculum for the 1st and 2nd-year medical students. Nicholl and Lou [15] argued that in their tutorless PBL model, it was important to provide as many opportunities as possible for formative assessment in order to monitor and adjust the development of the tutorless groups. We agree with their argument that ongoing and immediate formative assessment is valuable in tutorless PBL. Recent case reports have suggested that the use of pre-set cues, particularly pictures and videos [14] or e-learning resources [11] can help conduct effective tutorless PBL. To improve tutorless PBL, these new learning resources can positively contribute to students' self-contentment with their learning experience.

A possible reason why WES and SCS did not significantly differ between the tutorless and tutored groups may be because students in the tutorless group communicated with those in the tutored group after every SGD, thereby allowing students in the tutorless group to get some information from those in the tutored group. This helped in decreasing the gap in learning outcomes between both groups. This may also prompt peer-assisted learning for students in both groups. Ross and Cameron [23] argued that peer-assisted learning is an efficient and effective way of preparing medical students for their future role as educators. Although little attention has been paid to the effects of peer-assisted learning in medical schools [24], the positive effects of peer-assisted learning in medical education is gaining notoriety [24,25]. Although there have been no studies comparing tutorless PBL to student-tutored PBL, it appears that the effect of peer-assisted learning in student-tutored PBL is higher than that of tutored and tutorless PBL; however, a mixed course, including tutorless and tutored PBL, has unique characteristics as well as the potential to provide good learning outcomes.

There are two primary limitations to the current study. First, we were unable to develop other methods of measuring the effects of group learning and could measure only self-evaluation of group dynamics and attentiveness. The other types of evaluations such as peer evaluation may be more important in the tutorless group. Second limitation relates to the setting (four SGDs in a week session) and period (pre-clinical students), in which this study was conducted. Usually PBL tutorials are conducted in the first and second sessions with two to three days time for self study. A curriculum in which the SGD frequency is reduced during each session would be required. Moust et al. [26] reported that students in faculty-led PBL performed better than those in peer-facilitated groups during essay examinations designed to assess higher-order cognitive skills. Thus, we completed PBL2 for the third- and forth-year students as a tutored PBL course. More research on the cognitive effects of tutorless PBL for medical students during their clinical years is required.

Conclusions

Tutorless PBL can potentially produce learning outcomes that are comparable to tutored PBL; however, tutorless PBL is different from faculty/staff-tutored PBL and student-tutored PBL. Tutorless PBL has been used when PBL conducted in large classrooms [6,8,11,12,15]. However, tutorless PBL should not be easily used in the same way as student-tutored PBL because of the difficulty in maintaining faculty tutors or learning rooms. An appropriate and effective curriculum can be administered in every school by combining tutored PBL and student-tutored PBL

or tutorless PBL. We encourage the implementation of PBL in schools because this will potentially lead to further developments in the area of PBL.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
SH conducted all studies, performed statistical analyses and drafted the manuscript. KT and CI helped draft and critically appraise the manuscript. YF was involved in the conceptualisation of the study and participated in its design and coordination. All authors read and approved the final manuscript.

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INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Whole-body Insulin Resistance is Associated with Elevated Serum α-fetoprotein Levels in Patients with Chronic Hepatitis C

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Abstract

Objective Little is known about the relationship between elevated serum α-fetoprotein (AFP) levels and insulin resistance, which adversely influence the clinical course of chronic hepatitis C (CHC). Therefore, we investigated the association between serum AFP and insulin resistance in patients with CHC.

Methods We retrospectively investigated 300 patients with CHC without hepatoma who underwent liver biopsies and oral glucose tolerance tests. Patients taking antidiabetic drugs were excluded. We analyzed factors associated with elevated AFP levels (≥10.0 ng/mL) in 265 eligible patients. Twenty patients with a homeostasis model assessment for insulin resistance value of ≥2.0 and a whole-body insulin sensitivity index of <5.0 received prospective lifestyle intervention.

Results A univariate analysis showed that the body mass index, platelet count, levels of albumin, aspartate aminotransferase, alanine aminotransferase and γ-glutamyl transpeptidase, glucose metabolism, hepatic inflammation, fibrosis and steatosis were associated with elevated AFP levels. In a multivariate analysis, a platelet count of $<15\times10^4/\mu L$, aspartate aminotransferase level of ≥50 IU/L, γ-glutamyl transpeptidase level of ≥35 IU/L, whole-body insulin sensitivity index of <5.0 and stage 3-4 fibrosis were independently associated with an elevated AFP level. A Bayesian Network analysis showed that the aspartate aminotransferase level, whole-body insulin sensitivity index and hepatic fibrosis were directly associated with an elevated AFP level. The lifestyle intervention significantly improved the serum AFP level, homeostasis model assessment for insulin resistance and whole-body insulin sensitivity index.

Conclusion Whole-body insulin resistance is associated with an elevated serum AFP level in patients with CHC. Lifestyle interventions targeting insulin resistance can reduce the serum AFP level and may ameliorate the clinical course of CHC.

Key words: α-fetoprotein, hepatitis C, whole-body insulin resistance, Bayesian Network analysis, lifestyle intervention

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Introduction

Approximately 170 million people worldwide have persistent hepatitis C virus (HCV) infection (1), the leading cause of liver cirrhosis and hepatocellular carcinoma [HCC (2, 3)]. The serum α-fetoprotein (AFP) level is an important predictor of the clinical course in patients with chronic hepatitis C (CHC), as elevated serum AFP levels are associated with a low viral response rate to interferon [IFN (4)], advanced fibrosis (5-7) and a high frequency of HCC (6, 8-10). Although IFN can lead to biochemical improvement and eradi-

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cation of HCV, which reduces the risk of HCC (11), the clinical impact of HCV eradication on HCC prevention is less significant in older patients than in younger patients (8). Nevertheless, prolonged IFN therapy can decrease the serum AFP levels and thus prevent hepatocarcinogenesis, even in elderly patients (10).

Recent studies have shown that insulin resistance (IR) in HCV-infected patients is associated with the response to antiviral therapy (12-15), progression of fibrosis (12, 16-18) and development of HCC (19). Although HCV itself can evoke hepatic IR (16) and systemic IR (20), we previously reported that visceral fat accumulation is more strongly associated with IR in patients with CHC than in patients with non-alcoholic fatty liver disease (21). Therefore, it is likely that reducing visceral fat via lifestyle modification can improve IR in HCV-infected patients.

These findings indicate that the serum AFP levels and IR indices, both of which are noninvasively assessed, are significantly associated with the clinical course in HCV-infected patients. However, little is known about the relationship between the serum AFP levels and IR in patients with CHC. Therefore, we conducted a retrospective study to identify clinical factors, including glucose metabolism and histologic findings, associated with high elevated serum AFP levels in HCV-infected patients with no evidence of HCC. We also conducted a pilot study to determine whether lifestyle modification can improve IR or other clinical factors, including the serum AFP levels, in patients with CHC.

Materials and Methods

Patients

We conducted a retrospective study of 300 HCV-infected patients with no evidence of HCC who visited Saga Medical School Hospital between January 2004 and March 2010. Patients who underwent a liver biopsy and a 75-g oral glucose tolerance test (OGTT) were included in the analysis, while patients taking antidiabetic drugs were excluded. We set the cutoff value for AFP as 10.0 ng/mL because an even slightly elevated AFP level is a risk factor for HCC (6, 9). We analyzed factors associated with elevated AFP levels (≥10.0 ng/mL) in 265 patients who met these criteria, including 137 men and 128 women, with a median age of 58 years (range: 24-75 years).

Between June 2007 and March 2009, we conducted a pilot study to investigate whether lifestyle intervention can improve IR or other clinical factors, including the serum AFP levels, in patients with CHC. Only patients with no evidence of HCC whose homeostasis model assessment for insulin resistance (HOMA-IR) value was ≥2.0 (15) were enrolled. There were 11 men and nine women, with a median age of 60 years (range: 37-71 years). The whole-body insulin sensitivity index (WBISI) was <5.0 in all 20 patients. The study protocol was approved by the Institutional Review Board of Saga Medical School Hospital in accordance with the ethical guidelines of the Declaration of Helsinki (1975, as revised in 1983), and written informed consent was obtained from all patients.

Clinical and laboratory assessments

All demographic and laboratory data were collected at the time of the liver biopsy. In the pilot study, some data were also collected after the intervention. The demographic data included sex, age, body mass index (BMI; kg/m^2), alcohol consumption and history of IFN therapy. Alcohol consumption was classified into three groups: none, occasionally (<140 g/week) or regularly (≥140 g/week). Venous blood samples were obtained after a 12-hour overnight fast for hematology and blood chemistry examinations. The serum AFP level (ng/mL) was measured using a chemiluminescent immunoassay kit (Abbott Japan, Tokyo, Japan). For the OGTT, the patients ingested a solution containing 75 g of glucose, and venous blood samples were collected at 0, 30, 60, 90 and 120 minutes to measure the plasma glucose (PG; mg/dL) and serum insulin (SI; μU/mL) levels. The PG levels were determined using the glucokinase method and the SI levels were measured using a chemiluminescent immunoassay kit (Abbott Japan). Glucose tolerance was evaluated according to the World Health Organization criteria (22). Briefly, normal glucose tolerance (NGT) was defined as a fasting PG (FPG) level of <110 mg/dL and a 2-hour PG level of <140 mg/dL. Impaired fasting glycemia (IFG) was defined as an FPG level of 110-126 mg/dL and a 2-hour PG level of <140 mg/dL. Impaired glucose tolerance (IGT) was defined as an FPG level of <126 mg/dL and a 2-hour PG level of 140-200 mg/dL. Diabetes mellitus (DM) was defined as an FPG level of ≥126 mg/dL or a 2-hour PG level of ≥200 mg/dL. The indices of basal insulin secretion and insulin sensitivity were evaluated using the homeostasis model assessment (HOMA) method (23), as follows:

β cell function (HOMA-β) = fasting SI (FSI) ×360/[FPG-63]

Insulin resistance (HOMA-IR) = FPG × FSI/405

The WBISI (24) was calculated as $10,000/(\text{FPG} \times \text{FSI} \times \text{mean PG 0-120} \times \text{mean SI 0-120})^{0.5}$.

In the pilot study, we also measured the serum adiponectin (μg/mL), leptin (ng/mL) and soluble tumor necrosis factor receptor 2 (sTNFR2; pg/mL) levels before and after the lifestyle intervention using a Human Adiponectin ELISA Kit (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan), a Human Leptin RIA Kit (Millipore Corporation, Billerica, MA, USA) and a Quantikine Human sTNFRII/TNFRSF1B Immunoassay (R&D SYSTEMS Inc., Minneapolis, MN, USA).

Among the patients who underwent abdominal computed tomography, the visceral fat area (VFA; cm^2) was measured at the umbilical level and calculated using the Fat Scan software program [N2 Systems, Osaka, Japan (25)].

Liver histology

A percutaneous liver biopsy was performed using a Super-Core™ Biopsy Instrument (Medical Device Technolo-

gies, Inc., Gainesville, FL, USA) under ultrasound guidance. In each patient, a 15-mm-long liver biopsy specimen was fixed in 10% formalin, embedded in paraffin, sectioned and stained with Hematoxylin and Eosin staining and Azan for a histologic evaluation. The degree of histologic hepatic fibrosis and inflammation was scored using the METAVIR scoring system (26). Based on the degree of lymphocyte infiltration and hepatocyte necrosis, the level of inflammation was classified from A0 to A3, with a higher score indicating more severe inflammation. Fibrosis was graded from F0 to F4 as follows: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa without cirrhosis; and F4, cirrhosis. Steatosis was quantified as the percentage of hepatocytes that contained fat droplets classified into three groups: <5%, 5-30% and ≥30%.

Lifestyle intervention

The ideal body weight (kg) was calculated as 22× [height (m)]^2. A dietitian instructed each patient to maintain a total calorie intake of 25-35 kcal/ideal body weight/day according to the level of daily activity. The exercise intervention was based on the 'Exercise and Physical Activity Guide for Health Promotion 2006' published by the Ministry of Health, Labour and Welfare of Japan (27). Briefly, the patients were recommended to walk a minimum of 8,000 steps every day on flat terrain while wearing a pedometer. The patients were also instructed to record their diet and exercise activities in a diary. The lifestyle intervention was continued for >3 months with the goal of reducing the HOMA-IR to <2.0. In patients with limited improvements in IR, the intervention was discontinued at the discretion of the attending physician.

Statistical analysis

Continuous variables are presented as the median (range). Comparisons between groups were made using the Mann-Whitney *U* test for continuous variables and the χ^2 test or Fisher's exact probability test for categorical data. A multiple logistic regression analysis was used to identify factors independently associated with an elevated serum AFP level. Wilcoxon's signed-rank test was performed to analyze the paired samples. Values of $p<0.05$ were considered to be statistically significant.

A Bayesian Network (28, 29) is a directed acyclic graph that represents a joint probability distribution for a set of variables. Each node on the graph represents a variable, and a link between two nodes indicates a direct dependency between the variables. In the retrospective study, we used a Bayesian Network analysis to identify factors directly associated with an elevated serum AFP level.

Results

Retrospective study

The prevalence of an elevated AFP level (≥10 ng/mL) was 22.3% (59/265). Table 1 shows the characteristics of the patients stratified according to the serum AFP level (<10 vs. ≥10 ng/mL). A univariate analysis showed that BMI, the platelet count, the aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), triglyceride, high-density lipoprotein cholesterol (HDL-C) and albumin levels, HOMA-IR, WBISI, visceral obesity, hepatic inflammation, fibrosis and steatosis were associated with an elevated AFP level (Table 1). Variables with $p<0.01$ were used in the multiple logistic regression analysis. In terms of glucose metabolic factors, we included WBISI, as this factor was more strongly associated with the serum AFP level than the other indices. The VFA was excluded from this analysis because data were missing for a number of patients. The multiple logistic regression analysis showed that a platelet count of $<15\times10^4/\mu L$ (odds ratio [OR]: 2.74, 95% confidence interval [CI]: 1.27-5.91, p=0.01), an AST level of ≥50 IU/L (OR: 3.46, 95% CI: 1.24-9.65, p=0.018), a γ-GTP level of ≥35 IU/L (OR: 2.43, 95% CI: 1.03-5.71, p=0.042), a WBISI of <5.0 (OR: 3.55, 95% CI: 1.56-8.09, p=0.003) and stage 3-4 fibrosis (OR: 3.71, 95% CI: 1.43-9.58, p=0.007) were independently associated with an elevated AFP level (Table 2). The prevalence of an elevated AFP level according to the WBISI and fibrosis was 8.3% (11/133) and 36.4% (48/132) for a WBISI of ≥5.0 and <5.0, respectively, and 14.7% (33/224) and 63.4% (26/41) for fibrosis stage 0-2 and 3-4, respectively (Fig. 1). For the Bayesian Network analysis, we selected BMI, which affects metabolic factors, as well as the variables included in the multiple logistic regression analysis. The Bayesian Network analysis revealed that AST, WBISI and hepatic fibrosis were directly associated with an elevated AFP level (Fig. 2). Under conditions of AST ≥50 IU/L, WBISI <5.0 and fibrosis stage 3-4, 85% of the patients were presumed to have an elevated serum AFP level. On the other hand, when AST was ≥50 IU/L and fibrosis was stage 3-4, 71% of the patients with WBISI ≥5.0 were presumed to have a low serum AFP level (Table 3).

Pilot study

The median duration of the intervention was 182 days (range: 91-380 days). The baseline characteristics of the patients included in the prospective study and the changes in parameters after the lifestyle intervention are presented in Table 4. The VFA (p=0.001) and BMI (p<0.001) decreased significantly after the lifestyle intervention. The leptin/adiponectin ratio decreased (p=0.028) along with the reduction of visceral fat. In terms of hematology and biochemical data, the platelet count (p=0.026) and levels of γ-GTP (p=0.04), total cholesterol (p=0.042), triglycerides (p=0.008), creatinine (p=0.025), total protein (p=0.006) and albumin (p=0.004) decreased. Among the markers of glucose metabolism, FPG (p<0.001), FSI (p=0.001) and HOMA-IR (p<0.001) decreased after the intervention, while WBISI increased [p<0.001 (Fig. 3)]. The serum AFP level also decreased significantly after the intervention [p=0.002 (Fig. 3)].

Table 1. Characteristics of Patients according to the Serum α-fetoprotein Levels

	AFP < 10 ng/mL n = 206	AFP ≥ 10 ng/mL n = 59	p value
Males/females	105/101	32/27	0.768
Age (years)	58 (24–75)	59 (39–74)	0.170
BMI (kg/m^2)	22.9 (15.7–33.8)	23.7 (17.9–31.1)	0.033
Alcohol intake, none/occasionally/regularly/unknown	73/71/54/8	27/15/14/3	0.437
History of IFN therapy, yes/no/unknown	54/148/4	21/37/1	0.370
Platelet count (× 10^4/μL)	16.7 (5.5–42.2)	12.8 (5.7–25.2)	< 0.001
AST (IU/L)	40 (17–163)	68 (15–233)	< 0.001
ALT (IU/L)	43 (9–395)	75 (19–243)	< 0.001
γ-GTP (IU/L)	30 (3–509)	60 (13–323)	< 0.001
Total cholesterol (mg/dL)	176 (94–314)	169 (83–242)	0.093
Triglyceride (mg/dL)	87 (36–607)	104 (49–245)	0.002
HDL-C (mg/dL)	49 (23–108)[a]	43 (24–79)[b]	0.016
Uric acid (mg/dL)	5.4 (2.4–10.5)[c]	5.8 (2.1–8.1)[d]	0.194
Creatinine (mg/dL)	0.7 (0.5–1.9)	0.7 (0.3–1.4)	0.348
Total protein (g/dL)	7.2 (5.9–9.9)	7.2 (5.7–8.6)	0.530
Albumin (g/dL)	4.2 (3.2–5.2)	4.0 (2.7–4.7)	< 0.001
FPG (mg/dL)	87 (67–133)	88 (75–118)	0.867
2-h glucose (mg/dL)	117 (57–338)	136 (85–305)	< 0.001
FSI (μU/mL)	7 (2–24)	11 (3–34)	< 0.001
2-h insulin (μU/mL)	47 (6–500)	93 (20–294)	< 0.001
HOMA-IR	1.4 (0.3–7.7)	2.4 (0.6–8.0)	< 0.001
WBISI	5.6 (1.2–23.3)	2.9 (1.0–12.3)	< 0.001
HOMA-β	99 (24–630)	148 (41–666)	< 0.001
Glucose tolerance: NGT/non-NGT	149/57	30/29	0.003
VFA (cm^2)	60 (10–221)[e]	94 (12–163)[f]	< 0.001
Liver histology			
Inflammation: A0/A1/A2/A3	8/132/63/3	0/19/31/9	< 0.001
Fibrosis: F0/F1/F2/F3/F4	10/125/56/14/1	0/12/21/23/3	< 0.001
Steatosis (%): < 5/5–30/≥ 30	159/42/5	36/15/8	0.012

Values are median (range) or number of patients. BMI: body mass index, IFN: interferon, AFP: α-fetoprotein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: γ-glutamyl transpeptidase, HDL-C: high-density lipoprotein cholesterol, FPG: fasting plasma glucose, FSI: fasting serum insulin, HOMA-IR: homeostasis model assessment for insulin resistance, WBISI: whole-body insulin sensitivity index, HOMA-β: homeostasis model assessment for β cell function, NGT: normal glucose tolerance, VFA: visceral fat area. [a]n = 195, [b]n = 56, [c]n = 204, [d]n = 58, [e]n = 119, [f]n = 40.

Table 2. Factors Associated with Elevated Serum α-fetoprotein Level (Multiple Logistic Regression Analysis)

Variables	OR	95% CI	p value
Platelet < 15 × 10^4/μL	2.74	1.27–5.91	0.010
AST ≥ 50 IU/L	3.46	1.24–9.65	0.018
ALT ≥ 50 IU/L	0.68	0.24–1.98	0.482
γ-GTP ≥ 35 IU/L	2.43	1.03–5.71	0.042
Triglyceride ≥ 90 mg/dL	1.18	0.55–2.55	0.670
Albumin < 4 g/dL	0.86	0.37–1.98	0.724
WBISI < 5.0	3.55	1.56–8.09	0.003
Hepatic inflammation A2–A3	1.84	0.85–4.00	0.124
Hepatic fibrosis F3–F4	3.71	1.43–9.58	0.007

AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: γ-glutamyl transpeptidase, WBISI: whole-body insulin sensitivity index

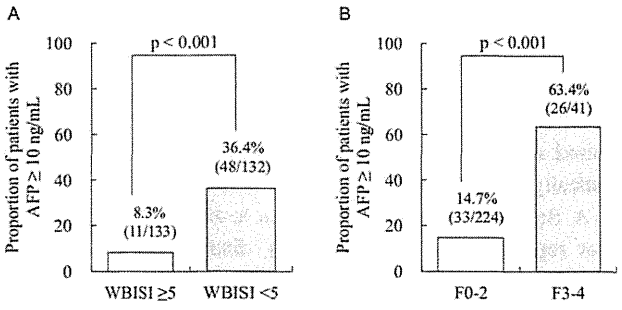

Figure 1. Prevalence of an elevated α-fetoprotein level (≥10 ng/mL) according to the (A) whole-body insulin sensitivity index and (B) hepatic fibrosis. AFP: α-fetoprotein, WBISI: whole-body insulin sensitivity index