International Journal of Hematology
https://doi.org/10.1007/s12185-024-03896-9

PROGRESS IN HEMATOLOGY

DIC Clinical Practice Guidelines 2024

Clinical practice guidelines for management of disseminated intravascular coagulation in Japan 2024. Part 1: sepsis

Kazuma Yamakawa[1] · Kohji Okamoto[2] · Yoshinobu Seki[3] · Takayuki Ikezoe[4] · Takashi Ito[5] · Toshiaki Iba[6] · Satoshi Gando[7] · Noritaka Ushio[1] · Takaaki Totoki[1] · Takeshi Wada[8] · Hidesaku Asakura[9] · Hiroyasu Ishikura[10] · Mitsuhiro Uchiba[11] · Toshimasa Uchiyama[12] · Kaoru Kawasaki[13] · Noriaki Kawano[14] · Shigeki Kushimoto[15] · Shin Koga[16] · Yuichiro Sakamoto[17] · Toshihisa Tamura[18] · Kenji Nishio[19] · Mineji Hayakawa[8] · Takeshi Matsumoto[20] · Seiji Madoiwa[21] · Toshihiko Mayumi[22] · Shinya Yamada[9] · Hideo Wada[23] · Committee of the Clinical Practice Guidelines for Management of Disseminated Intravascular Coagulation 2024, the Japanese Society on Thrombosis and Hemostasis

Received: 17 October 2024 / Revised: 29 November 2024 / Accepted: 1 December 2024

Abstract
The Japanese Society on Thrombosis and Hemostasis (JSTH) published the first-ever disseminated intravascular coagulation (DIC) guidelines in 2009. Fifteen years later, the JSTH developed new guidelines covering DIC associated with various underlying conditions. These guidelines were developed in accordance with the GRADE system to determine the strength of the recommendations and certainty of the evidence. This article was drafted as Part 1 of an overall DIC guideline covering various underlying conditions, with sepsis as the subject. In this section, seven key clinical issues (questions) are set. Question 1, regarding DIC diagnosis, introduces several diagnostic criteria, such as the JAAM-2, ISTH overt, SIC, and JSTH DIC criteria and recommends choosing the appropriate diagnostic criteria for DIC based on an understanding of their diagnostic properties. For pharmacotherapy in DIC patients with sepsis, we recommend the administration of antithrombin (Question 2) and recombinant thrombomodulin (Question 3) (both GRADE 1B). However, we do not make a clear recommendation regarding the administration of heparin (Question 6) and serine protease inhibitors (Question 7) because of the lack of evidence. Combination therapy, order of administration, and other administration methods for antithrombin and recombinant thrombomodulin are proposed as important future research questions (Questions 4 and 5).

Keywords Antithrombin · DIC · Infection · Sepsis · Thrombomodulin

Introduction

Japan has played a leading role in basic and clinical research on disseminated intravascular coagulation (DIC), as well as in the development of diagnostic criteria and treatment guidelines. The Scientific and Standardization Committee on DIC of the Japanese Society on Thrombosis and Hemostasis (JSTH) first published the DIC guidelines in 2009, titled "Expert consensus for the treatment of disseminated intravascular coagulation in Japan" [1], followed by a supplementary version in 2014 [2]. The committee selected members from various specialties, including hematology, emergency medicine, surgery, intensive care, and laboratory medicine, to systematically review the pathophysiology, diagnosis, and treatment of DIC. Although it mainly focused on DIC associated with infections, this consensus was a pioneering initiative, providing recommendations primarily for DIC in the field of internal medicine, particularly in hematology and infectious diseases. Thereafter, internationally, the British Committee for Standards in Haematology published guidelines in 2009 [3], and the Italian Society on Thrombosis and Hemostasis published guidelines in 2012 [4]. The Scientific and Standardization Committee on DIC of the International Society on Thrombosis and Hemostasis (ISTH) worked to harmonize the three guidelines [5].

After 6 years of the publication of the supplementary Japanese guidelines, there was a growing demand for guidelines

Extended author information available on the last page of the article

Published online: 16 December 2024

that addressed DIC treatment for different underlying conditions beyond infections. Although there was some high-quality evidence for DIC associated with infections (sepsis), there was also evidence for underlying conditions, such as hematologic malignancies, solid tumors, and obstetrics, as well as evidence of DIC associated with trauma, acute pancreatitis, acute liver failure, vascular abnormalities, venom, and other rare underlying conditions. It has been recognized that large-scale randomized clinical trials (RCTs) for DIC associated with rare diseases are challenging to conduct; thus, developing evidence-based guidelines would be difficult. This is because there is a lack of evidence that clinical guidelines are necessary for these diseases.

We formed the Committee of the Clinical Practice Guidelines for Management of DIC 2024 and developed new guidelines covering DIC associated with various underlying conditions based on the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system. This article was drafted as Part 1 of an overall DIC guideline covering various underlying conditions; the target condition was sepsis. Other domains are referred to in alternative articles.

Overview and basic principles of this clinical practice guideline

Purpose of the guideline

These guidelines aim to facilitate prompt and appropriate diagnosis, initiate treatment, improve therapeutic efficacy, and ultimately improve the clinical outcomes of patients with DIC caused by various underlying conditions. As the pathophysiology of DIC varies based on the underlying disease, the goal was also to enhance the understanding of the DIC condition and its management, and provide information on rare underling conditions of DIC.

Users of this clinical practice guideline

This includes all healthcare professionals, such as physicians, nurses, pharmacists, and paramedics, who provide DIC care in clinical settings. Other healthcare providers, patients receiving DIC care, and their families have also benefited from the information provided.

Target patient population for the recommendations

The target population includes all patients receiving DIC care. This also includes patients with conditions that are likely to be complicated because of DIC.

Notes on the use of this guideline

These guidelines are intended only as a standard treatment and expert consensus guide at the time of publication. As each patient's condition and the system of healthcare facilities differ, the choice of treatment strategy should be determined through personalized discussions between healthcare professionals and patients. These guidelines are not intended to force treatment or restrict healthcare professionals' discretion.

Classification and designation of the questions

Table 1 shows the classification and designation of the questions in these Guidelines.

Methods of preparing this clinical practice guideline

Developing organization

The Committee of the Clinical Practice Guidelines for the Management of DIC was established under the Board of the JSTH to develop these guidelines. Five hematologists, two transfusion specialists, two laboratory specialists, eight emergency physicians, two surgeons, two general physicians, one obstetrician, and one basic researcher were recruited by members of the Scientific and Standardization Committee of DIC of the JSTH.

Table 1 Categories of questions in this guideline

Category	Definition of question category
Background question	Question regarding fundamental topics of clinical importance among basic knowledge (clinical characteristics, epidemiological characteristics, and clinical flow) and contents generally accepted in clinical practice
Clinical question	Among the foreground questions based on important clinical issues, questions for which a systematic review was completed, and an evidence-based recommendation can be provided
Future research question	Among the foreground questions based on important clinical issues, question for which an evidence-based recommendation could not be provided owing to lack of evidence, etc. Research topics to be resolved in the future are proposed

Fundamental policy for the preparation of this guideline

The Clinical Practice Guidelines for Management of DIC in Japan 2024 were prepared in accordance with the "Minds Manual for Guideline Development 2017 and 2020" [6] to determine the strength of recommendations and certainty of the evidence. We conducted a systematic review of each question and made recommendations based on evidence. In principle, the rationale for the recommendation of the question was determined by assessing the balance of benefits and harms, and considering the patient's preferences and situation, healthcare economics (including medical insurance), social conditions, and other factors.

Scope and question planning

In developing the guidelines, a draft scope was proposed by each underlying disease-working group and approved by the entire committee. Subsequent key clinical issues were decided upon, as necessary. Questions were formulated for each underlying disease group. The reasonableness of each question was discussed and approved at a plenary committee meeting as the final version.

Literature search and adoption criteria

A literature search was conducted until December 31, 2021, using PubMed, Cochrane Library, Scopus, and ICHUSHI. During the preparation process, we added new articles as they were published as new evidence. The literature was screened for each underlying disease group and adopted for evaluation in the systematic review.

Adoption criteria

(i) RCTs comparing DIC treatment drugs should be adopted with the highest priority.
(ii) If i) does not exist or there is little evidence, non-randomized trials, single-arm studies, case–control studies, and observational studies that allow data extraction should be adopted.
(iii) In rare disease-working groups where evidence is particularly limited, case series and case reports should be adopted.

Systematic review and data extraction

Each underlying disease-working group determined the outcomes of "benefit" and "harm" for each question. The importance of the outcomes was scored. The systematic review team evaluated individual studies according to a predefined PICO and decided on the studies to be adopted. Data on the risk of bias and each outcome were extracted, a quantitative (or qualitative) systematic review was conducted, and a systematic review report was prepared.

Evaluation of the certainty of evidence and drafting

We assessed the certainty of evidence using the GRADE approach and rated the certainty for each outcome as high (A), moderate (B), low (C), or very low (D) based on the following eight factors of the GRADE: five factors that might lead to a rating down of the certainty of evidence (risk of bias [RoB], inconsistency, indirectness, imprecision, and publication bias), and three factors that might lead to the rating up (large effect, plausible confounding, and dose response gradient).

The overall certainty of the evidence regarding the overall outcomes for the questions was determined while considering the total body of evidence. A draft recommendation was developed after carefully considering the balance between benefits and harm, patient values and preferences, and healthcare economics and resources, including the health insurance system.

Formulation of recommendations and consensus building

A plenary committee meeting was held, and all draft recommendations were reviewed. Consensus formation was based on web-based voting using the GRADE Grid and a recommendation was determined as consensus formation when 70% or more of the votes were assigned to a specific recommendation category. If the consensus criteria were not reached after the first vote, a second vote was obtained after consultation. If, after discussion, the draft did not receive more than 70% agreement, the recommendation was as assigned a "weak" recommendation in cases where there was agreement on the direction of the recommendation, and "no recommendation" in cases where the direction of the recommendation was varied.

The Panel graded the strength of the recommendations as strong or conditional (for or against the intervention of interest). For future research and background questions, the strength of the recommendation and certainty of evidence were not stated, the draft statements were reviewed in plenary committee meetings, and the final version was decided through discussion and voting.

Dissemination and revision of this guideline

After the publication of this guideline, the Scientific and Standardization Committee of DIC of the JSTH will continue to review the contents and promote and disseminate the guidelines. Furthermore, we will conduct a questionnaire

survey of the society's members, survey the dissemination of the guidelines, define the clinical indicators, and assess the usefulness of the guidelines.

Recommendations and their rationales

The questions and recommendations are summarized in Table 2.

Question 1 (BQ): How should DIC associated with sepsis be diagnosed?

Statement

- There are several diagnostic criteria for DIC associated with sepsis, including Japanese Association for Acute Medicine (JAAM) DIC criteria, SIC (sepsis-induced coagulopathy) criteria, International Society on Thrombosis and Haemostasis (ISTH) overt DIC criteria, and Japanese Society on Thrombosis and Hemostasis (JSTH) DIC criteria (Table 3).
- We recommend choosing the appropriate diagnostic criteria for DIC based on an understanding of the diagnostic properties of each one.

Rationale

DIC is classified into two distinct categories: compensated non-overt DIC and uncompensated overt DIC. In Japan, the ISTH criteria for the diagnosis of overt DIC [7] has been widely employed to diagnose the non-compensated phase. The acute-phase DIC criteria of the JAAM have been used to diagnose the compensated phase [8]. Recently, the Systemic Inflammatory Response Syndrome (SIRS) score, a component of the JAAM DIC diagnostic criteria, has not been employed in routine clinical practice. Thus, the JAAM DIC diagnostic criteria were modified to the JAAM-2 criteria [9], which no longer includes the SIRS score. The ISTH released the SIC criteria for diagnosing DIC in the compensated phase in 2019 [10]. These criteria advocate a two-stage approach for the diagnosis of sepsis-associated DIC, SIC, and overt DIC. In addition, the JSTH proposed novel diagnostic criteria for DIC in 2017 [11]. In this approach, the diagnosis of infectious DIC incorporates molecular markers, such as antithrombin activity, thrombin/antithrombin complex, soluble fibrin, prothrombin fragment1 + 2 in addition to conventional markers, such as platelet count, fibrinogen/fibrin degradation products and prothrombin time ratio. Molecular markers are thought to be more sensitive and

Table 2 Summary of questions and recommendations

Question 1	How should DIC associated with sepsis be diagnosed?
Statement	There are several diagnostic criteria for DIC associated with sepsis, including the Japanese Association for Acute Medicine (JAAM) DIC criteria, SIC (sepsis-induced coagulopathy) criteria, International Society on Thrombosis and Haemostasis (ISTH) overt DIC criteria, and Japanese Society on Thrombosis and Hemostasis (JSTH) DIC criteria We recommend choosing the appropriate diagnostic criteria for DIC based on an understanding of the diagnostic properties of each one
Question 2	Should antithrombin be administered to patients with DIC associated with sepsis?
Recommendation	We recommend antithrombin administration to patients with DIC associated with sepsis (strong recommendation/moderate certainty of evidence: GRADE 1B)
Question 3	Should recombinant thrombomodulin be administered to patients with DIC associated with sepsis?
Recommendation	We recommend recombinant thrombomodulin administration to patients with DIC associated with sepsis (strong recommendation/moderate certainty of evidence: GRADE 1B)
Question 4	Should combination therapy of antithrombin and recombinant thrombomodulin be used for patients with DIC associated with sepsis?
Statement	We have not made clear recommendations on combination therapy of antithrombin and recombinant thrombomodulin for patients with DIC associated with sepsis
Question 5	Which should be administered first to patients with DIC associated with sepsis: antithrombin or recombinant thrombomodulin?
Statement	We have not made a clear recommendation on whether to administer antithrombin or recombinant thrombomodulin first to patients with DIC associated with sepsis
Question 6	Should unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) be administered to patients with DIC associated with sepsis?
Statement	We have not made a clear recommendation on UFH or LMWH administration for patients with DIC associated with sepsis
Question 7	Should serine protease inhibitors be administered to patients with DIC associated with sepsis?
Statement	We have not made a clear recommendation on serine protease inhibitors administration for patients with DIC associated with sepsis

Table 3 JAAM-2 DIC, SIC, ISTH overt DIC, and JSTH DIC scoring systems

	Points	JAAM-2 DIC (ref. 9)	Sepsis-induced coagulopathy (ref. 10)	ISTH overt DIC (ref. 7)	JSTH DIC (infectious type) (ref. 11)
Platelet count	3	$<80\times10^9$/L or > 50% decrease/24 h	–	–	$\leq50\times10^9$/L
	2	–	$<100\times10^9$/L	$<50\times10^9$/L	$>50, \leq80\times10^9$/L
	1	$\geq80, <120\times10^9$/L or 30–50% decrease/24 h	$\geq100, <150\times10^9$/L	$\geq50, <100\times10^9$/L	$>80, \leq120\times10^9$/L
FDP (or D-dimer)	3	≥ 25 μg/mL	–	Strong increase	≥ 40 μg/mL
	2	–	–	Moderate increase	$\geq20, <40$ μg/mL
	1	$\geq10, <25$ μg/mL	–	–	$\geq10, <20$ μg/mL
Prothrombin time (sec)	2	–	> 1.4	≥ 6 s	≥ 1.67
Prothrombin time ratio	1	≥ 1.2	$>1.2, \leq1.4$	$\geq3, <6$ s	$\geq1.25, <1.67$
Fibrinogen	1	–	–	< 100 g/mL	–
Antithrombin	1	–	–	–	≤ 70%
TAT, SF or F1 + 2	1	–	–	–	≥ Twofold increase
SOFA score [a]	2	–	≥ 2	–	–
	1	–	1	–	-
Liver failure	−3	–	–	–	Yes
Required points for criteria-positive		3 points	2 points	5 points	6 points

[a]SOFA score is assessed by the sum of the four items (respiratory SOFA, cardiovascular SOFA, hepatic SOFA, and renal SOFA)

JAAM Japanese Association for Acute Medicine, *ISTH* International Society on Thrombosis and Haemostasis, *JS*TH Japanese Society on Thrombosis and Hemostasis, *DIC* disseminated intravascular coagulation, *FDP* fibrin degradation products, *TAT* thrombin-antithrombin complex, *SF* soluble fibrin, *F1 + 2* prothrombin fragment 1 + 2, *SOFA* Sequential Organ Failure Assessment

specific than conventional markers; however, their wider use is currently limited by a lack of acceptance in clinical settings.

In summary, the diagnostic criteria for sepsis-associated DIC include the JAAM-2 DIC, SIC, ISTH overt, and JSTH DIC diagnostic criteria (Table 3). It is recommended that the most appropriate method be selected based on an understanding of the characteristics of each component, as previously mentioned.

Question 2 (CQ): Should antithrombin be administered to patients with DIC associated with sepsis?

Recommendation

- We recommend antithrombin administration to patients with DIC associated with sepsis (strong recommendation/moderate certainty of evidence: GRADE 1B).

Background

Antithrombin exerts anticoagulant effects by inhibiting thrombin and activated factor X. Additionally, it exerts anti-inflammatory effects by regulating prostacyclin production by vascular endothelial cells, rendering it a potentially efficacious treatment for sepsis-associated DIC. In Japan, antithrombin is indicated for use in patients with DIC with an antithrombin activity of 70% or lower, and it is widely used in clinical practice. However, previous reports have yielded conflicting results regarding its effectiveness in improving the prognosis of patients with sepsis-associated DIC. Therefore, this is of great clinical significance for the formulation of this question.

Recommendation rationale

- Balance between benefits and harm.

There were five RCTs [12–16] with the adopted evidence. Forest plots of these comparisons are shown in Fig. 1. As a primary outcome, moderate effects were expected for all-cause mortality (a decrease of 147 per 1000). As secondary outcomes, there was no increase in the incidence of serious bleeding complications (increase of 8 per 1000) and increase in the DIC resolution (increase of 448 per 1000). Based on the above findings, it was determined that the benefits of antithrombin administration outweigh those of DIC in patients with sepsis.

- Certainty of evidence.

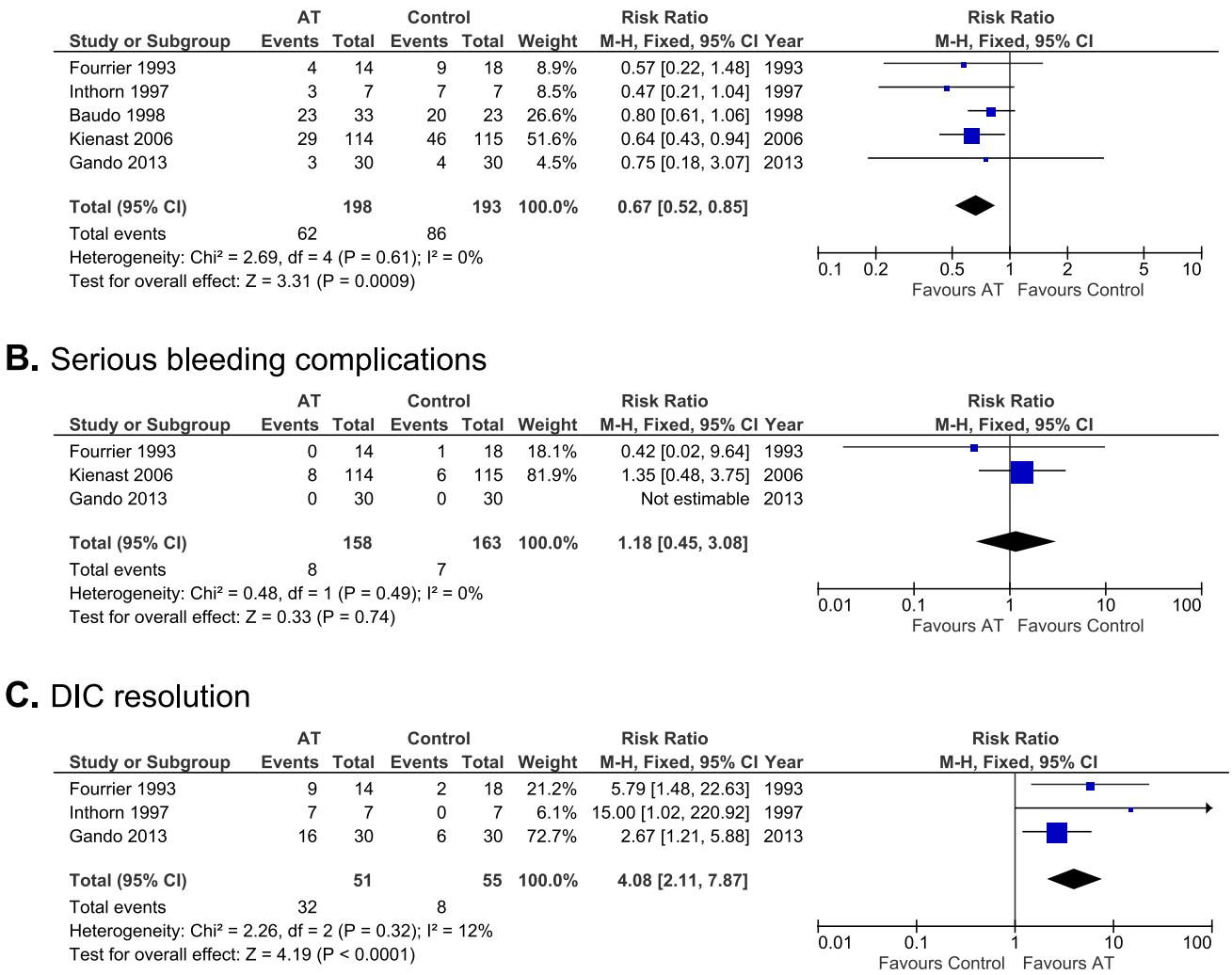

Fig. 1 Forest plot of the comparison: antithrombin versus control (Question 2). **A** All-cause mortality, **B** serious bleeding complication, **C** DIC resolution. *AT* antithrombin, *M–H* Mantel–Haenszel, *CI* confidence interval

The certainty of evidence for each outcome ranged from "low" to "moderate," as shown in Table 4. Considering the direction, the overall certainty of the evidence was judged to be "moderate."

- Other ancillary matters.

The appropriate AT activity level for AT administration is unclear, however, it should be administered when the level is 70% or lower, as recognized by insurance coverage in Japan. A future international phase II randomized trial of antithrombin in patients with sepsis is currently in being scheduled [17]. Recommendations may change owing to the accumulation of evidence in the future.

Discussion and decision by voting

First vote: Strong recommendation to use: 7/11 (64%); weak recommendation to use: 4/11 (36%).

Second vote: Strong recommendation to use: 10/12 (83%); weak recommendation to use: 2/12 (17%).

Question 3 (CQ): Should recombinant thrombomodulin be administered to patients with DIC associated with sepsis?

Recommendation

- We recommend recombinant thrombomodulin administration to patients with DIC associated with sepsis

Table 4 GRADE evidence profile: antithrombin administration for sepsis-associated DIC (Question 2)

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antithrombin	Control	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality												
5	Randomized trials	Not serious	Not serious	Not serious	Serious	None	62/198 (31.3%)	86/193 (44.6%)	RR 0.67 (0.52–0.85)	147 fewer per 1000 (247 fewer to 67 fewer)	⨁⨁⨁◯ MODERATE	Critical
Serious bleeding complications												
3	Randomized trials	Not serious	Not serious	Not serious	Very serious	None	8/158 (5.1%)	7/163 (4.3%)	RR 1.18 (0.45–3.08)	8 more per 1000 (24 fewer to 89 more)	⨁⨁◯◯ LOW	Critical
DIC resolution												
3	Randomized trials	Not serious	Not serious	Not serious	Serious	None	32/51 (62.7%)	8/55 (14.5%)	RR 4.08 (2.11–7.87)	448 more per 1000 (161 more to 999 more)	⨁⨁⨁◯ MODERATE	Important

GRADE Grading of Evidence, Assessment, Development and Evaluation, *CI* confidence interval, *RR* risk ratio

(strong recommendation/moderate certainty of evidence: GRADE 1B).

Background

Recombinant thrombomodulin has been demonstrated to exert anticoagulant effects by binding to thrombin and activating protein C. Additionally, it possesses anti-inflammatory properties via its lectin-like domains. The results of a multinational phase III study (the SCARLET trial) were published in 2019, but no definitive conclusions were drawn. The use of this treatment is still debated in clinical practice, and the formulation of this question is considered of great clinical significance.

Recommendation rationale

- Balance between benefits and harm

There were four RCTs [18–21] with the adopted evidence. The forest plots of the comparisons are shown in Fig. 2. As a primary outcome, mild effects were expected for all-cause mortality (decrease of 39 per 1000). As secondary outcomes, there was no increase in the incidence of serious bleeding complications (increase of 12 per 1000) and increase in the DIC resolution (increase of 120 per 1000). Based on the above findings, it was determined that the benefits of recombinant thrombomodulin administration outweigh those of DIC in patients associated with sepsis.

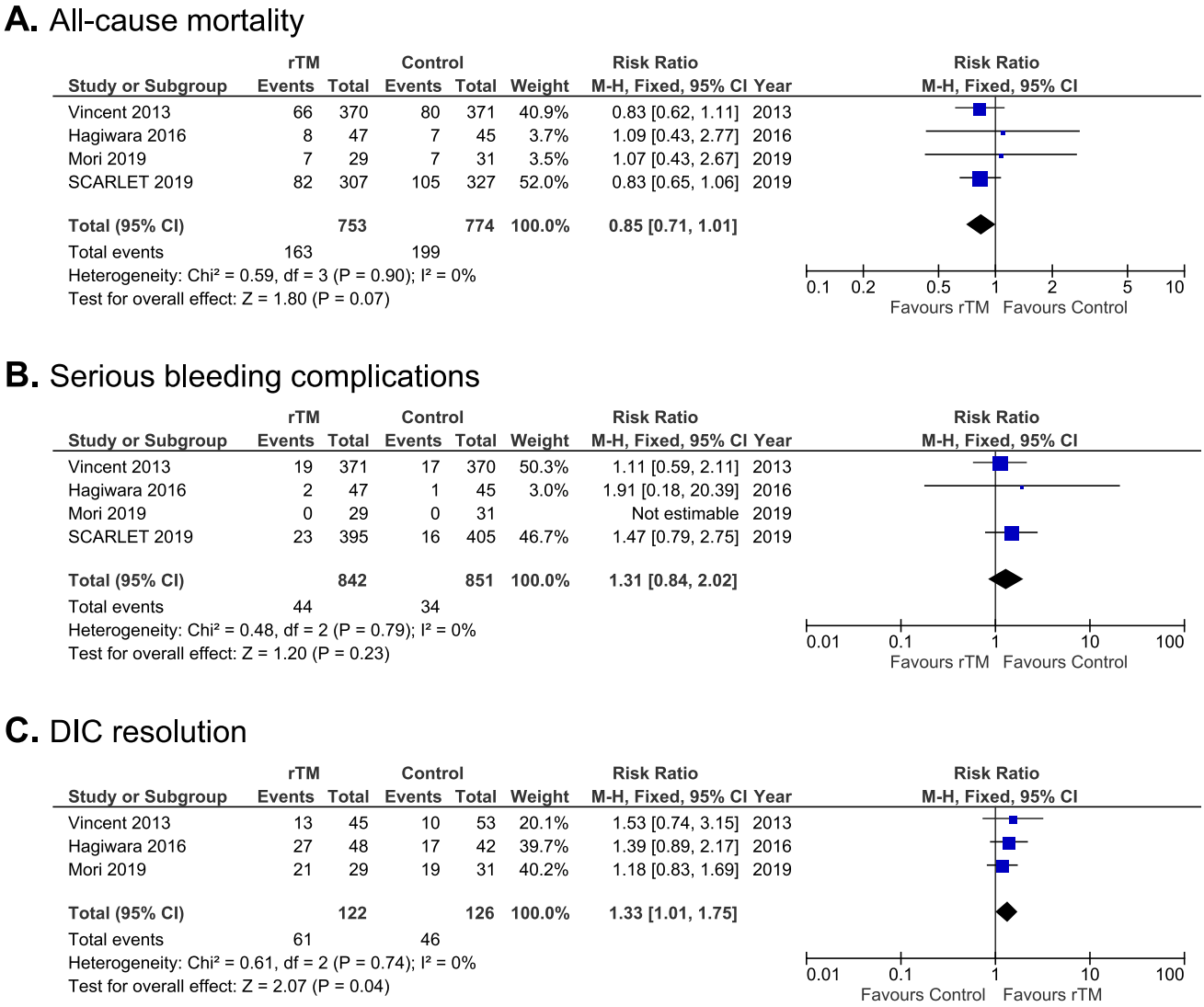

Fig. 2 Forest plot of the comparison: recombinant thrombomodulin versus control (Question 3). **A** all-cause mortality, **B** serious bleeding complication, **C** DIC resolution. *rTM* recombinant thrombomodulin, *M–H* Mantel–Haenszel, *rTM* recombinant thrombomodulin, *CI* confidence interval

- Certainty of evidence

The certainty of evidence for all outcomes was "moderate," as shown in Table 5. Considering the direction, the overall certainty of the evidence was judged to be "moderate."

Discussion and decision by voting

First vote: Strong recommendation to use: 1011 (91%); weak recommendation to use: 1/11 (9%); One abstention was observed due to conflict of interest.

Question 4 (FRQ): Should combination therapy of antithrombin and recombinant thrombomodulin be used for patients with DIC associated with sepsis?

Statement

- We have not made clear recommendations on whether a combination therapy of antithrombin and recombinant thrombomodulin be used for patients with DIC associated with sepsis.

Rationale

In clinical situations, in Japan, antithrombin and recombinant thrombomodulin are occasionally concomitantly administered, although evidence on the effectiveness and safety of the combined use of these agents is limited. These two anticoagulants have different mechanisms of action, and their combined use may enhance their anticoagulant effects [22], However, it is possible that irreversible inhibition of thrombin by antithrombin may interfere with the activation of protein C by the thrombomodulin/thrombin complex [23]. Animal model studies suggest that combination therapy may improve survival compared to antithrombin or recombinant thrombomodulin alone [24].

To date, no RCTs have been conducted comparing the use of antithrombin or recombinant thrombomodulin alone versus combination therapy for sepsis-associated DIC. A systematic review of observational studies demonstrated a trend toward improved survival with combination therapy with antithrombin and recombinant thrombomodulin [25]. Bleeding complications were similar between the combination therapy and monotherapy groups. In the future, more evidence from RCTs or high-quality observational studies are warranted to clarify the usefulness of combination therapy and the optimal patient population for combination therapy.

Question 5 (FRQ): Which should be administered first to patients with DIC associated with sepsis—antithrombin or recombinant thrombomodulin?

Statement

- We have not made a clear recommendation on whether to administer antithrombin or recombinant thrombomodulin first to patients with DIC associated with sepsis.

Rationale

The administration of antithrombin or recombinant thrombomodulin for sepsis-associated DIC is recommended in both this guideline and the Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020 [26]. However, there is no consensus on which of these two agents should be administered first.

None of the 11 observational studies that evaluated the combination of antithrombin and recombinant thrombomodulin for sepsis-associated DIC addressed the timing of administration of either of these agents [25]; neither basic nor clinical research has been conducted on this issue. Further evidence from RCTs or high-quality observational studies is required to determine the order of priority of their use.

Question 6 (FRQ). Should unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) be administered to patients with DIC associated with sepsis?

Statement

- We have not made a clear recommendation on UFH or LMWH administration for patients with DIC associated with sepsis.

Rationale

Heparin binds to antithrombin and inhibits thrombin and activated factor X to exert anticoagulant activity. It is expected to be effective in the treatment of DIC associated with sepsis, which causes organ failure owing to circulatory disturbances caused by excessive coagulation activation. The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020 weakly recommends that UFH/LMWH should not be used as a standard treatment for sepsis-associated DIC [26]. Currently, there is no high-quality evidence of the efficacy of UFH/LMWH for DIC, including two RCTs [27, 28].

Recently, a meta-analysis showed the benefits of UFH and LMWH in patients with sepsis, including DIC associated with sepsis [29, 30]. The benefits of heparin for coagulation

Table 5 GRADE evidence profile: recombinant thrombomodulin administration for sepsis-associated DIC (Question 3)

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rTM	Control	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality												
4	Randomized trials	Not serious	Not serious	Not serious	Serious	None	163/753 (21.6%)	199/774 (25.7%)	RR 0.85 (0.71–1.01)	39 fewer per 1000 (75 fewer to 3 more)	⨁⨁⨁◯ MODERATE	Critical
Serious bleeding complications												
4	Randomized trials	Not serious	Not serious	Not serious	Serious	None	44/842 (5.2%)	34/851 (4.0%)	RR 1.31 (0.84–2.02)	12 more per 1000 (6 fewer to 41 more)	⨁⨁⨁◯ MODERATE	Critical
DIC resolution												
3	Randomized trials	Not serious	Not serious	Not serious	Serious	None	61/122 (50.0%)	46/126 (36.5%)	RR 1.33 (1.01–1.75)	120 more per 1000 (4 more to 274 more)	⨁⨁⨁◯ MODERATE	Important

GRADE Grading of Evidence, Assessment, Development, and Evaluation, *rhTM* recombinant thrombomodulin, *CI* confidence interval, *RR* risk ratio

disorders in COVID-19 have been recognized worldwide [31, 32]. Otherwise, future evaluations of the effectiveness of UFH and LMWH in sepsis-associated DIC are warranted.

Question 7 (FRQ): Should serine protease inhibitors be administered to patients with DIC associated with sepsis?

Statement

- We have not made a clear recommendation on serine protease inhibitors' administration to patients with DIC associated with sepsis.

Rationale

Serine protease inhibitors are considered to have a lower risk of bleeding complications compared to other anticoagulants because of their combined effects of inhibiting fibrinolytic activity and excessive coagulation activity in patients with DIC. It has a long history of use in clinical settings in Japan to treat DIC caused by various underlying diseases, including sepsis. Gabexate and nafamostat mesylates are used as insurance agents for DIC in Japan.

The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020 weakly recommends that serine protease inhibitors should not be used as a standard treatment for sepsis-associated DIC [26]. Two RCTs provide a rationale for this [33, 34]. Both studies examined gabexate mesylate; however, they were small studies containing only 20–50 patients and did not prove its benefit. Twenty years have passed since then and there is no high-quality evidence on the effect of proteolytic enzyme inhibitors on DIC. Based on these findings, these guidelines do not provide recommendations for serine protease inhibitors.

Funding These clinical practice guidelines were prepared with funding from the Japanese Society on Thrombosis and Hemostasis. None of the members received any reward for their work.

Data availability Not available.

Declarations

Conflict of interest Kazuma Yamakawa has received research grants from the Japan Blood Products Organization and Asahi Kasei Pharma. Yoshinobu Seki was involved in clinical trials conducted by Chugai Pharmaceutical. Takashi Ito has received lecture fees and research grants from Asahi Kasei Pharma. Toshiaki Iba received a research grant from JIMRO. Hiroyasu Ishikura has received lecture fees from Asahi Kasei Pharma. Hideo Wada received a research grant from I.L. Japan. Hidesaku Asakura is editor of International Journal of Hematology. None of the authors have any potential conflicts of interest to disclose.

References

1. Wada H, Asakura H, Okamoto K, Iba T, Uchiyama T, Kawasugi K, et al. Expert consensus for the treatment of disseminated intravascular coagulation in Japan. Thromb Res. 2010;125(1):6–11.
2. Wada H, Okamoto K, Iba T, Kushimoto S, Kawasugi K, Gando S, et al. Addition of recommendations for the use of recombinant human thrombomodulin to the "Expert consensus for the treatment of disseminated intravascular coagulation in Japan." Thromb Res. 2014;134(4):924–5.
3. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. Br J Haematol. 2009;145(1):24–33.
4. Di Nisio M, Baudo F, Cosmi B, D'Angelo A, De Gasperi A, Malato A, et al. Diagnosis and treatment of disseminated intravascular coagulation: guidelines of the Italian Society for Haemostasis and Thrombosis (SISET). Thromb Res. 2012;129(5):e177–84.
5. Wada H, Thachil J, Di Nisio M, Mathew P, Kurosawa S, Gando S, et al. Guidance for diagnosis and treatment of DIC from harmonization of the recommendations from three guidelines. J Thromb Haemost. 2013;11(4):761–7.
6. Minds Manual Developing Committee. Minds manual for guideline development 2020 ver. 3.0. Tokyo: Japan Council for Quality Health Care; 2021.
7. Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M. Scientific subcommittee on disseminated intravascular coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH): towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost. 2001;86(5):1327–30.
8. Gando S, Iba T, Eguchi Y, Ohtomo Y, Okamoto K, Koseki K, et al. A multicenter, prospective validation of disseminated intravascular coagulation diagnostic criteria for critically ill patients: comparing current criteria. Crit Care Med. 2006;34(3):625–31.
9. Yamakawa K, Umemura Y, Mochizuki K, Matsuoka T, Wada T, Hayakawa M, et al. Proposal and validation of a clinically relevant modification of the Japanese association for acute medicine disseminated intravascular coagulation diagnostic criteria for sepsis. Thromb Haemost. 2024;124(11):1003–12.
10. Iba T, Levy JH, Yamakawa K, Thachil J, Warkentin TE, Levi M, et al. Proposal of a two-step process for the diagnosis of sepsis-induced disseminated intravascular coagulation. J Thromb Haemost. 2019;17(8):1265–8.
11. Asakura H, Takahashi H, Uchiyama T, Eguchi Y, Okamoto K, Kawasugi K, et al. Proposal for new diagnostic criteria for DIC from the Japanese society on thrombosis and hemostasis. Thromb J. 2016;14:42.
12. Fourrier F, Chopin C, Huart JJ, Runge I, Caron C, Goudemand J. Double-blind, placebo-controlled trial of antithrombin III concentrates in septic shock with disseminated intravascular coagulation. Chest. 1993;104:882–8.
13. Inthorn D, Hoffmann JN, Hartl WH, Mühlbayer D, Jochum M. Antithrombin III supplementation in severe sepsis: beneficial effects on organ dysfunction. Shock. 1997;8:328–34.
14. Baudo F, Caimi TM, de Cataldo F, Ravizza A, Arlati S, Casella G, et al. Antithrombin III (ATIII) replacement therapy in patients with sepsis and/or postsurgical complications: a controlled double-blind, randomized, multicenter study. Intensive Care Med. 1998;24:336–42.
15. Kienast J, Juers M, Wiedermann CJ, Hoffmann JN, Ostermann H, Strauss R, et al. Treatment effects of high-dose antithrombin without concomitant heparin in patients with severe sepsis with or without disseminated intravascular coagulation. J Thromb Haemost. 2006;4:90–7.

16. Gando S, Saitoh D, Ishikura H, Ueyama M, Otomo Y, Oda S, et al. A randomized, controlled, multicenter trial of the effects of antithrombin on disseminated intravascular coagulation in patients with sepsis. Crit Care. 2013;17:R297.
17. https://endpointhealth.com/news/endpoint-health-enters-into-global-collaboration-and-licensing-agreement-with-grifols/
18. Vincent JL, Ramesh MK, Ernest D, LaRosa SP, Pachl J, Aikawa N, et al. A randomized, double-blind, placebo-controlled, Phase 2b study to evaluate the safety and efficacy of recombinant human soluble thrombomodulin, ART-123, in patients with sepsis and suspected disseminated intravascular coagulation. Crit Care Med. 2013;41:2069–79.
19. Hagiwara A, Tanaka N, Uemura T, Matsuda W, Kimura A. Can recombinant human thrombomodulin increase survival among patients with severe septic-induced disseminated intravascular coagulation: a single-centre, open-label, randomised controlled trial. BMJ Open. 2016;6: e012850.
20. Mori S, Ai T, Sera T, Ochiai K, Otomo Y. Human soluble recombinant thrombomodulin, ART-123, resolved early phase coagulopathies, but did not significantly alter the 28 day outcome in the treatment of DIC associated with infectious systemic inflammatory response syndromes. J Clin Med. 2019;8:1553.
21. Vincent JL, Francois B, Zabolotskikh I, Daga MK, Lascarrou JB, Kirov MY, et al. Effect of a recombinant human soluble thrombomodulin on mortality in patients with sepsis-associated coagulopathy: the SCARLET randomized clinical trial. JAMA. 2019;321:1993–2002.
22. Ito T, Kakuuchi M, Maruyama I. Endotheliopathy in septic conditions: mechanistic insight into intravascular coagulation. Crit Care. 2021;25(1):95.
23. Arishima T, Ito T, Yasuda T, Yashima N, Furubeppu H, Kamikokuryo C, et al. Circulating activated protein C levels are not increased in septic patients treated with recombinant human soluble thrombomodulin. Thromb J. 2018;16:24.
24. Iba T, Miki T, Hashiguchi N, Tabe Y, Nagaoka I. Combination of antithrombin and recombinant thrombomodulin modulates neutrophil cell-death and decreases circulating DAMPs levels in endotoxemic rats. Thromb Res. 2014;134(1):169–73.
25. Totoki T, Makino Y, Yamakawa K, Koami H, Wada T, Ito T, et al. Effects of combination therapy of antithrombin and thrombomodulin for sepsis-associated disseminated intravascular coagulation: a systematic review and meta-analysis. Thromb J. 2024;22(1):10.
26. Egi M, Ogura H, Yatabe T, Atagi K, Inoue S, Iba T, et al. The Japanese clinical practice guidelines for management of sepsis and septic shock 2020 (J-SSCG 2020). Acute Med Surg. 2021;8(1): e659.
27. Liu XL, Wang XZ, Liu XX, Hao D, Jaladat Y, Lu F, et al. Low-dose heparin as treatment for early disseminated intravascular coagulation during sepsis: a prospective clinical study. Exp Ther Med. 2014;7(3):604–8.
28. Yang C, Chen X, Zheng D, Chen L, Ding Y, Xie W. Impacts of early anticoagulant therapy on tissue perfusion in patients with sepsis. Int J Clin Exp Med. 2016;9(10):20074–9.
29. Fu S, Yu S, Wang L, Ma X, Li X. Unfractionated heparin improves the clinical efficacy in adult sepsis patients: a systematic review and meta-analysis. BMC Anesthesiol. 2022;22(1):28.
30. Li X, Liu Z, Luo M, Xi Y, Li C, Wang S, et al. Therapeutic effect of low-molecular-weight heparin on adult sepsis: a meta-analysis. Ann Palliat Med. 2021;10(3):3115–27.
31. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020;18(5):1023–6.
32. Iba T, Levy JH, Levi M, Thachil J. Coagulopathy in COVID-19. J Thromb Haemost. 2020;18(9):2103–9.
33. Nishiyama T, Matsukawa T, Hanaoka K. Is protease inhibitor a choice for the treatment of pre- or mild disseminated intravascular coagulation? Crit Care Med. 2000;28:1419–22.
34. Hsu JT, Chen HM, Chiu DF, Chen JC, Huang CJ, Hwang TL, et al. Efficacy of gabexate mesylate on disseminated intravascular coagulation as a complication of infection developing after abdominal surgery. J Formos Med Assoc. 2004;103:678–84.

Authors and Affiliations

Kazuma Yamakawa[1] · Kohji Okamoto[2] · Yoshinobu Seki[3] · Takayuki Ikezoe[4] · Takashi Ito[5] · Toshiaki Iba[6] · Satoshi Gando[7] · Noritaka Ushio[1] · Takaaki Totoki[1] · Takeshi Wada[8] · Hidesaku Asakura[9] · Hiroyasu Ishikura[10] · Mitsuhiro Uchiba[11] · Toshimasa Uchiyama[12] · Kaoru Kawasaki[13] · Noriaki Kawano[14] · Shigeki Kushimoto[15] · Shin Koga[16] · Yuichiro Sakamoto[17] · Toshihisa Tamura[18] · Kenji Nishio[19] · Mineji Hayakawa[8] · Takeshi Matsumoto[20] · Seiji Madoiwa[21] · Toshihiko Mayumi[22] · Shinya Yamada[9] · Hideo Wada[23] · Committee of the Clinical Practice Guidelines for Management of Disseminated Intravascular Coagulation 2024, the Japanese Society on Thrombosis and Hemostasis

✉ Kazuma Yamakawa
kazuma.yamakawa@ompu.ac.jp

[1] Department of Emergency and Critical Care Medicine, Osaka Medical and Pharmaceutical University, 2-7 Daigakumachi, Takatsuki, Osaka 569-8686, Japan

[2] Department of Surgery, Kitakyushu City Yahata Hospital, Kitakyushu, Japan

[3] Department of Hematology, Niigata University Medical and Dental Hospital, Niigata, Japan

[4] Department of Hematology, Fukushima Medical University School of Medicine, Fukushima, Japan

[5] Department of Hematology and Immunology, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan

[6] Department of Emergency and Disaster Medicine, Juntendo University Graduate School of Medicine, Bunkyo-ku, Tokyo, Japan

[7] Department of Acute and Critical Care Medicine, Sapporo Higashi Tokushukai Hospital, Sapporo, Japan

[8] Division of Acute and Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Hokkaido University Faculty of Medicine, Sapporo, Japan

[9] Department of Hematology, Kanazawa University Hospital, Kanazawa, Japan

[10] Department of Emergency and Critical Care Medicine, Faculty of Medicine, Fukuoka University, Fukuoka, Japan

[11] Department of Blood Transfusion and Cell Therapy, Kumamoto University Hospital, Kumamoto, Japan

[12] Department of Laboratory Medicine, NHO Takasaki General Medical Center, Takasaki, Japan

[13] Department of Obstetrics and Gynecology, Kindai University Faculty of Medicine, Higashiosaka, Japan

[14] Department of Internal Medicine, Miyazaki Prefectural Miyazaki Hospital, Miyazaki, Japan

[15] Division of Emergency and Critical Care Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

[16] Department of Internal Medicine, SBS Shizuoka Health Promotion Center, Shizuoka, Japan

[17] Department of Emergency and Critical Care Medicine, Faculty of Medicine, Saga University, Saga, Japan

[18] Department of Surgery 1, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

[19] Department of General Medicine, Uda Municipal Hospital, Nara, Japan

[20] Department of Transfusion Medicine and Cell Therapy, Mie University Hospital, Tsu, Japan

[21] Department of Clinical Laboratory Medicine, Tokyo Saiseikai Central Hospital, Minato-ku, Tokyo, Japan

[22] Department Intensive Care, Japan Community Healthcare Organization Chukyo Hospital, Nagoya, Japan

[23] Associated Department with Mie Graduate School of Medicine, Mie Prefectural General Medical Center, Yokkaichi, Japan