Efficacy of recombinant human soluble thrombomodulin for acute exacerbation of idiopathic pulmonary fibrosis: A systematic review and meta-analysis

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Abstract. Idiopathic pulmonary fibrosis (IPF) is a chronic fibrosing lung disease of unknown etiology. Recombinant human soluble thrombomodulin (rhTM) is used for the management of acute exacerbation (AE) of IPF. The present review aimed to summarize the evidence and perform a meta-analysis of the efficacy and safety of rhTM in the management of AE-IPF. An electronic search of titles and abstracts published until 31st August 2019 was performed in the PubMed, Biomed Central, Scopus and Embase databases. Studies comparing rhTM-treated and control subjects with AE-IPF and assessing mortality and adverse events were included. Six studies met the inclusion criteria. A total of 145 patients received rhTM, while 146 patients served as controls. The meta-analysis indicated that rhTM resulted in a reduction in 28-day [odds ratio (OR), 0.25; 95% CI, 0.08-0.77; P=0.02; I^2=0%] and 90-day mortality (OR, 0.29; 95% CI, 0.17-0.49; P<0.00001; I^2=0%) compared with the controls. Adverse events were pooled and no difference was determined between rhTM and control groups (OR, 1.07; 95% CI, 0.45-2.51; P=0.88; I^2=0%). It was indicated that administration of rhTM may reduce the short-term mortality in patients with AE-IPF; however, the quality of evidence was not high. The drug appears to be safe without any enhanced risk of adverse events, although high-quality randomized controlled trials with a large sample size are required to further support its use in the treatment of IPF.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrosing lung disease of unknown etiology (1). IPF is associated with an increased fibroblast population, leading to excessive deposition of collagen in the lung alveolar spaces (1,2). This pathological change subsequently leads to decreased gas exchange and respiratory failure. While disease progression is usually slow, a number of patients experience acute deterioration of respiratory function, which is termed as acute exacerbation (AE) of IPF (AE-IPF) (2). In a retrospective review of 461 patients with IPF in South Korea, the 1- and 3-year incidences of AE-IPF were estimated to be 14.2 and 20.7%, respectively (3). While the exact etiology of AE-IPF remains elusive, the prognosis is poor, with a systematic review estimating the mortality rate to be 60% at 1 month and 67% at 3 months after disease onset (4).

The pathophysiology of AE-IPF has been attributed to procoagulant and antifibrinolytic activity in affected patients (3). Imokawa *et al* (5) demonstrated the strong presence of tissue factor, a coagulation initiator, in the lung tissues of patients with IPF. Kotani *et al* (6) have reported higher concentrations of plasminogen activator inhibitor (PAI)-1 and PAI-2 antigen levels in bronchoalveolar lavage (BAL) supernatant fluids and cell lysates, suggestive of an antifibrinolytic activity. While one study corroborate this theory based on improved survival of patients treated with low-molecular-weight heparin (7), another study indicated a lack of benefit of anticoagulant therapy in such patients (8). High-dose corticosteroids and immunosuppressive drugs, including cyclosporine A, have also been used for managing AE-IPF, but the clinical efficacy of these drugs is still under dispute (9,10).

Thrombomodulin, a transmembranous protein expressed on the surface of vascular endothelial cells, is an essential component in the regulation of intravascular coagulation (11). Due to its anticoagulant and anti-inflammatory effects, thrombomodulin has been successfully used in the management of disseminated intravascular coagulation (DIC) (11). Recombinant human soluble thrombomodulin (rhTM; Recomodulin; Asahi Kasei Pharma Corp.), which comprises only the extracellular domain of thrombomodulin, has also been explored in the management of various

respiratory, renal and cardiovascular diseases (12). Recently, several trials reported on the use of rhTM in the management of AE-IPF (13-15). While research is still at the nascent stage, there is a requirement to summarize the results of these multiple studies to evaluate the quality of evidence and provide a direction for further research. Therefore, the purpose of the present systematic review and meta-analysis was to evaluate the efficacy and safety of rhTM when used in the management of AE-IPF.

Materials and methods

Guidelines. The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (16) and the Cochrane Handbook for Systematic Reviews of Intervention (17) were followed during the preparation of this review.

Search strategy. An electronic search of titles and abstracts in the PubMed (https://pubmed.ncbi.nlm.nih.gov), Biomed Central (https://www.biomedcentral.com), Scopus (https://www.scopus.com/home.uri) and Embase (https://www.embase.com/login#search) databases was performed using the following key words: 'Recombinant human thrombomodulin', 'thrombomodulin', 'pulmonary fibrosis', 'AE', 'IPF' and 'clinical outcomes'. Titles were searched by two independent reviewers (BW and TL) with the last search performed on 31st August 2019. The reference lists of published studies and review articles on the subject were also searched for the identification of any further trials. After screening records by their titles and abstracts, the full texts of selected articles were retrieved. Each of the two reviewers assessed individual studies based on the inclusion criteria. Disagreements, if any, were resolved by discussion.

Study selection and outcomes. Using the common evidence medicine framework, population, intervention, comparison, outcome (18), all types of studies performed on patients with AE-IPF (*Population*) were included. Trials comparing rhTM (*Intervention*) vs. control (*Comparison*) for AE-IPF and assessing mortality and adverse events (*Outcomes*) were included in the review. Duplicate studies based on the same dataset, non-comparative studies, case series, case reports, review articles and studies that were not published in English language were excluded. In the case of studies with overlapping datasets, the study encompassing the largest dataset was selected.

Two independent reviewers retrieved data from selected studies using a standardized data collection form. The details sourced were the following: Authors, publication year, country of origin, sample size, baseline characteristics of study participants, treatment protocol, mortality and adverse events. The primary outcome of interest was the incidence of 28- and 90- day mortality. The secondary outcome was the incidence of adverse events.

Risk of bias assessment. The Risk of Bias Assessment Tool for Non-randomized Studies was used for quality assessment (19). Studies were rated as having low, high or unclear risk of bias regarding the following points: Selection of participants, confounding variables, measurement of exposure blinding of
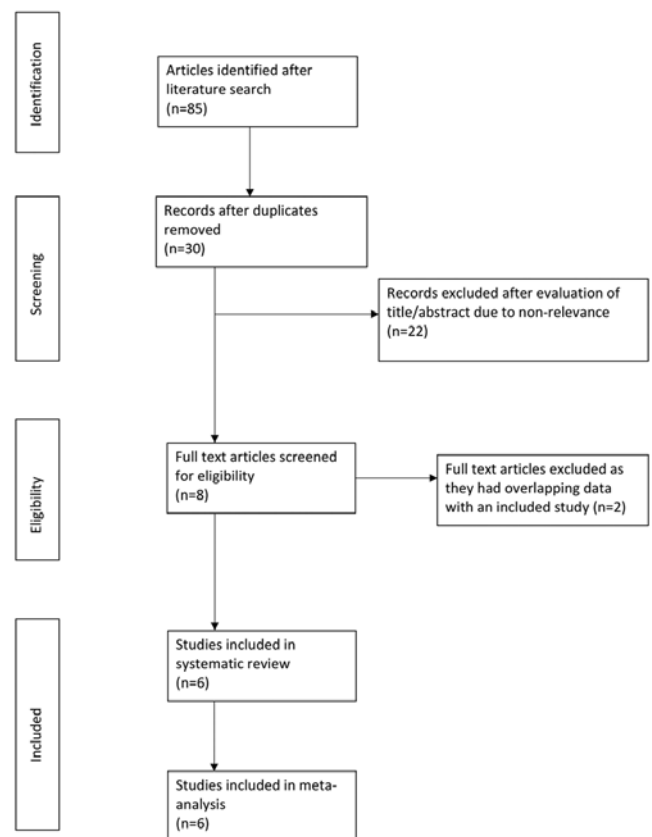

Figure 1. Study flow-chart.

outcome assessment, incomplete outcome data and selective outcome reporting.

Statistical analysis. RevMan version 5.3 (Cochrane Collaboration) was used for meta-analysis. Considering the methodological heterogeneity amongst studies, a random-effects model was used to calculate the pooled effect size. Data were summarised using the Mantel-Haenszel odds ratio (OR) with 95% CI. Inter-study heterogeneity was estimated using the I^2 statistic. I^2 values of 25-50% were considered to indicate low heterogeneity, 50-75% medium heterogeneity and >75% represented substantial heterogeneity.

Results

Literature search and study selection. The literature search yielded a total of 85 records. After the exclusion of duplicates, 30 unique articles were identified. The titles and abstracts of these 30 articles were then screened for possible inclusion in the present study. A total of 22 articles were excluded due to non-relevance and full texts of 8 articles were retrieved (Fig. 1). A total of three studies (19-21) had overlapping datasets, of which two (20,21) were excluded. A total of six studies (13-15, 21-23) were finally included in the present systematic review and meta-analysis.

Features of the studies included. Details of the studies included are presented in Table I. Two studies were retrospective studies (13,22) and three were single-arm prospective studies

Table I. Characteristics of included studies.

Authors (year)	Study type	Sample size		Age (years)		Treatment protocol	(Refs.)
		rhTM	Control	rhTM	Control		
Tsushima et al (2014)	Prospective with historical controls	20	6	76.2±0.4	73.7±1.2	rhTM group: MP pulse therapy at 1 g/day for 3 days, followed by prednisolone 1 mg/kg/day. rhTM (0.06 mg/kg/day) for 6 days. Control group: Similar treatment without rhTM.	(15)
Kataoka et al (2015)	Retrospective	20	20	73.5±NR	71.0±NR	rhTM group: MP pulse therapy at 1 g/day for 3 days with cyclosporine A 2.5 mg/kg/day followed by tapered dose of steroids. rhTM (0.06 mg/kg/day) for 6 days followed by continuous IV infusion of LMWH 750.000 IU/kg/day. LMWH discontinued if any adverse events were observed. Control group: Similar treatment without rhTM	(13)
Abe et al 2015	Prospective, non-randomized	11	11	68.9±7.3	73.1±11.3	rhTM group: MP pulse therapy at 1 g/day for 3 days with cyclophosphamide and/or cyclosporine A and 0.06 mg/kg/day rhTM for 6 days. Control group: Similar treatment without rhTM.	(24)
Hayakawa et al (2016)	Prospective with historical controls	10	13	73.2±9.5	69.7±8.5	rhTM group: MP pulse therapy at 1 g/day for 3 days, then 80 mg/day for 7 days with rhTM 380 U/kg/day for 30 min for 7 days. Concomitant administration of anticoagulants and immunosuppressants prohibited. Control group: Similar treatment without rhTM but no restriction of other drugs.	(14)
Sakamoto et al (2017)	Retrospective	45	35	75.0±NR	75.0±NR	rhTM group: MP pulse therapy at 1 g/day for 3 days with cyclosporine A 2.5 mg/kg/day in 66 patients, followed by tapered dose of steroids and 0.06 mg/kg/day rhTM for 6 days. Control group: Similar treatment without rhTM. Furthermore, 11 patients received LMWH 75 IU for 14 days.	(22)
Arai et al (2019)	Prospective with historical controls	39	61	74.0±NR	74.0±NR	rhTM group: Generally treated with IV MP for 3 days. Polymyxin B-immobilized fibre column therapy administered using toraymyxin. Anticoagulant and antiplatelet drugs used as required. rhTM (380 U/kg/day) for 6 days. Control group:Similar treatment without rhTM.	(23)

rhTM, recombinant human soluble thrombomodulin; NR, not reported; MP, methylprednisolone; LMWH, low-molecular-weight heparin; IU, international units; IV, intravenous; SD, standard deviation.

Table II. Baseline characteristics of participants of the studies included.

Parameters	Tsushima et al (15) rhTM	Tsushima et al (15) Control	Kataoka et al (13) rhTM	Kataoka et al (13) Control	Abe et al (24) rhTM	Abe et al (24) Control	Hayakawa et al (14) rhTM	Hayakawa et al (14) Control	Sakamoto et al (22) rhTM	Sakamoto et al (22) Control	Arai et al (23) rhTM	Arai et al (23) Control
PaO_2/FiO_2 (mmHg)	NR	NR	224.0±NR	238.0±NR	198.0±62	234.0±126	168.0±56	183.0±47	256.0±NR	260.0±NR	161.0±NR	194.6±NR
WBC count, (mm³)	14,000±462	15,820±291	10,350±NR	10,350±NR	14,590±6,031	9,518±2,835	NR	NR	10,500±NR	10,200±NR	10,200±NR	9,700±NR
LDH (IU/l)	782±41	477±13	300±NR	313±NR	430±148	419±150	378±118	444±173	353±NR	351±NR	349±NR	347±NR
CRP (mg/dl)	13.1±0.7	11.8±0.5	4.7±NR	6.8±NR	6.8±5.8	11.3±7.3	11.5±8.3	11±11.1	6.0±NR	6.9±NR	12.4±NR	9.1±NR
KL-6 (U/l)	1,812±111	1,956±218	1,278±NR	1,255±NR	2,018±780	1,489±1,385	1,512±583	2,060±1,520	1,299±NR	1,038±NR	1,192±NR	1,516±NR
SP-D (ng/ml)	NR	NR	202±NR	203±NR	759±638	338±338	482±527	676±711	288±NR	317±NR	NR	NR
D-dimer (mg/ml)	NR	NR	2.3±NR	2.4±NR	4.4±3.7	3.3±4.9	5.3±7.9	6.9±8.9	4.2±NR	4.8±NR	NR	NR
TAT (ng/ml)	34.7±1.4	24.2±2.2	NR	NR	9.1±11.0	14.8±22.7	8.1±13.5	NR	NR	NR	NR	NR
FDP (µg/ml)	99.0±11.0	39.6±7.4	NR	NR	8.6±4.7	8.4±5.6	NR	NR	8.8±NR	9.4±NR	NR	NR
PIC (ng/ml)	NR	NR	NR	NR	1.4±0.4	1.8±0.7	3.0±5.1	NR	NR	NR	NR	NR

rhTM, recombinant human soluble thrombomodulin; PaO_2, oxygen partial pressure; FiO_2, fraction of inspired oxygen; NR, not reported; WBC, white blood cell; LDH, lactate dehydrogenase; CRP, C-reactive protein; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein D; TAT, thrombin-antithrombin; FDP, fibrin/fibrinogen degradation products; PIC, plasmin inhibitor complex. Data presented as mean ± SD.

utilizing a historical control group (14,15,23), while one was a non-randomized prospective trial (24). All trials were performed in Japan. The sample size varied across the studies, with 6-61 participants per group. The baseline parameters of the experimental and control groups as reported by the studies are presented in Table II. The authors reported negligible differences in the baseline parameters between the rhTM and control groups. The dosage of rhTM was the same across the studies (0.06 mg/kg/day is equivalent to 380 U/kg/day). Methylprednisolone pulse therapy was administered for three days in all studies in the experimental and control groups.

Outcomes. The 28-day mortality rates were reported by three studies (14,15,24). Within the rhTM group, 29.26% of patients died, while 56.66% of patients died in the control group. The meta-analysis indicated that treatment with rhTM was associated with a significant reduction in 28-day mortality compared with that in the control group (OR, 0.25; 95% CI, 0.08-0.77; P=0.02; $I^2=0\%$; Fig. 2).

The 90-day mortality rates were reported by five (13,14,21-23) of the six studies included. A total of 125 patients received rhTM, while 140 patients served as controls. The overall 90-day mortality rate was 33.6% in the rhTM group and 62.85% in the control group. Pooled analysis indicated that rhTM significantly reduced the 90-day mortality in patients with AE-IPF (OR, 0.29; 95% CI, 0.17-0.49; P<0.00001; $I^2=0\%$; Fig. 3).

Data on adverse events were reported by five trials (13,14,21-23). Details of adverse events in the studies included are presented in Table III. Hayakawa *et al* (14) did not report any adverse events, while Sakamoto *et al* (22) reported only minor adverse events in the study group, which did not require discontinuation of treatment. Abe *et al* (24) reported one case of hepatic and renal failure in the study group. The authors suspected the cause of death in this patient to be a drug interaction between warfarin and cyclosporine, leading to uncontrolled serum levels of cyclosporine and subsequent renal and hepatic failure. Kataoka *et al* (13) reported hemorrhagic complications in the study and control groups, which were managed by discontinuation of rhTM and low-molecular-weight heparin, respectively. Arai *et al* (23) reported two cases of bleeding (1 case of gastrointestinal and 1 case of nasal) in the control group but no hemorrhagic complication in the rhTM group. All adverse events were pooled for a meta-analysis, which demonstrated no significant difference between the rhTM and control groups (OR, 1.07; 95% CI, 0.45-2.51; P=0.88; $I^2=0\%$; Fig. 4).

Risk of bias. The assessment of the risk of bias in the included studies is presented in Table IV. A high risk of bias was noted across all studies in the selection of participants, which were recruited at different time intervals in all trials.

Discussion

Several different therapies have been studied to improve outcomes in AE-IPF. These include corticosteroids, anti-coagulants, antacids, ambrisentan, imatinib, nintedanib, phosphodiesterase-5 inhibitors, pirfenidone, dual endothelin receptor antagonists (e.g. macitentan) and combination therapy

Table III. Adverse events reported by the studies included.

Study	rhTM	Control	(Ref.)
Tsushima *et al*	NR	NR	(15)
Kataoka *et al*	One case of hemosputum on day 5. and one case of acute DVT on day 4.	One case of bleeding from central venous catheter on day 3 and 1 case of subcutaneous bleeding on day 8.	(13)
Abe *et al*	One patient died of hepatic and renal failure due to high concentration of cyclosporine (suspected drug interaction with warfarin).	None.	(24)
Hayakawa *et al*	None.	None.	(14)
Sakamoto *et al*	Mild hemoptysis and hematuria in one patient on day 1. No case of serious bleeding.	None.	(22)
Arai *et al*	One case of gastrointestinal bleeding, one case of nasal bleeding, one case of DVT, one case of cerebral infarction, one case of drug-induced hepatitis, 1 case of an unspecified vascular event, one case of fungal infection.	Two cases of pneumomediastinum, one case of pneumothorax, three cases of DVT, one case of hepatitis B, one case of hepatitis B PCR positive, one case of sulfamethoxazole/trimethoprim, -associated thrombocytopenia, one case of MRSA pneumonia, one case of fungal infection.	(23)

rhTM, recombinant human soluble thrombomodulin; NR, not reported; DVT, deep vein thrombosis; MRSA, methicillin-resistant Staphylococcus aureus.

Table IV. Risk of bias summary.

| Study	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	(Ref.)
Tsushima *et al*	High risk	High risk	Low risk	Low risk	Low risk	Low risk	(15)
Kataoka *et al*	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	(13)
Abe *et al*	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	(24)
Hayakawa *et al*	High risk	High risk	Low risk	Low risk	Low risk	Low risk	(14)
Sakamoto *et al*	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	(22)
Arai *et al*	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	(23)
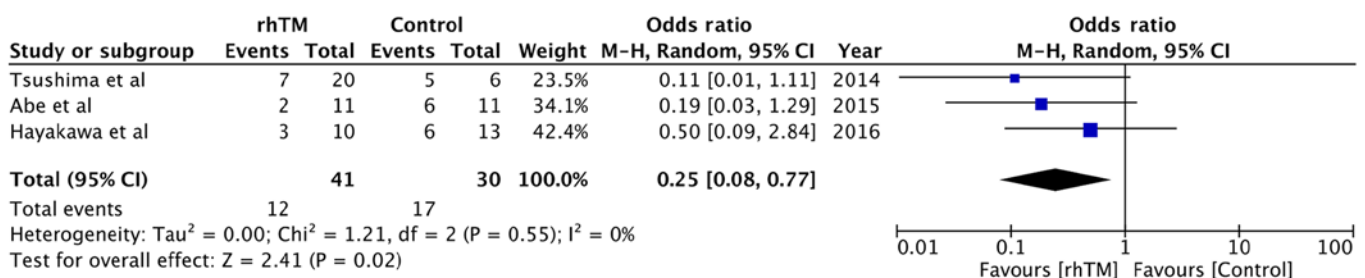
Figure 2. Forest plot for comparison of 28-day mortality between the rhTM and control groups. The black diamond denotes the point estimate and 95% CIs of the pooled data and indicates a 75% reduced odds of mortality with rhTM treatment. rhTM, recombinant human soluble thrombomodulin; df, degrees of freedom, M-H, Mantel-Haenszel.

of prednisone, azathioprine and N-acetylcysteine (25). Despite several attempted treatment strategies, no single management protocol has been accepted as the standard to date. The updated American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society guidelines do not recommend the use of warfarin, ambrisentan, imatinib or the combination therapy of prednisone, azathioprine and N-acetylcysteine, while providing a conditional recommendation for nintedanib, pirfenidone, macitentan and phosphodiesterase-5 inhibitors (25).
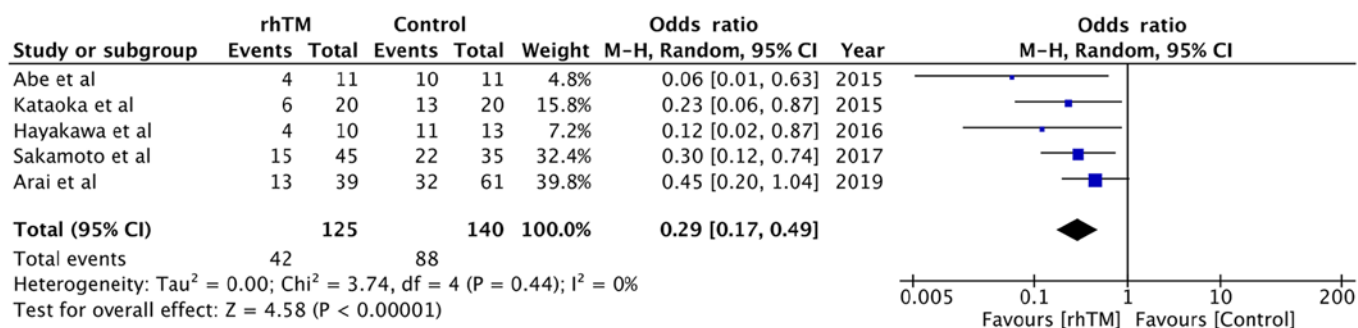
Figure 3. Forest plot for comparison of 90-day mortality between rhTM and control groups. The black diamond denotes the point estimate and 95% CI of the pooled data and indicates a 71% reduced odds of mortality with rhTM treatment. rhTM, recombinant human soluble thrombomodulin; df, degree of freedom; M-H, Mantel-Haenszel.
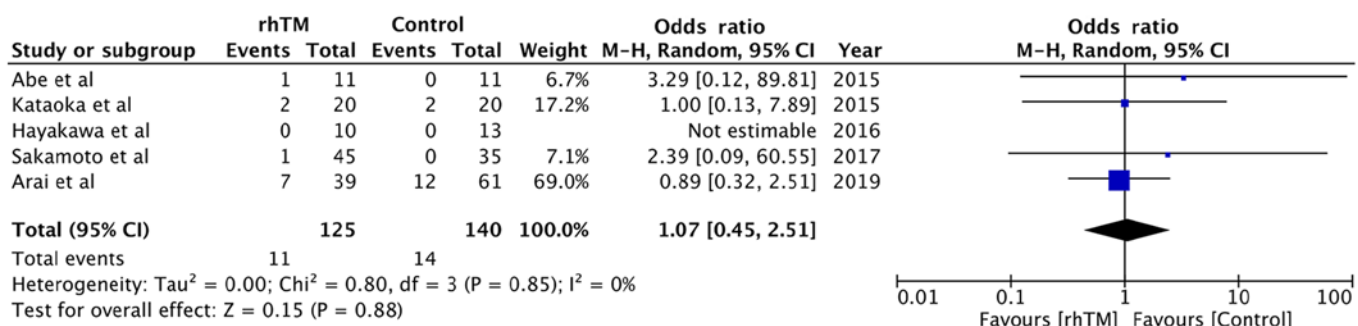

Figure 4. Forest plot for comparison of adverse events between rhTM and control groups. The black diamond denotes the point estimate and 95% CI of the pooled data and indicates that the odds of adverse events with rhTM was 1.07-fold of that in the control group, with no statistical significance. rhTM, recombinant human soluble thrombomodulin; df, degree of freedom; M-H, Mantel-Haenszel.

The use of immunosuppressants, including cyclophosphamides, cyclosporine or tacrolimus, has been examined, but only in small retrospective studies providing inconclusive evidence for the potential benefits of these drugs (9,26). In routine practice, administration of corticosteroids in the form of methylprednisolone pulse therapy is the most commonly employed management technique, despite low evidence supporting its use (27). Corticosteroid therapy was utilized in all six of the included studies of the present review but with disparity in the use of immunosuppressant drugs. Cyclophosphamide and/or cyclosporine were administered in three studies in the experimental and control groups, while in the clinical trial by Hayakawa et al (14), only the control group received immunosuppressants. The variance in the treatment strategies for AE-IPF may be attributed to the poorly understood pathophysiological mechanism of the disease.

In an attempt to elucidate the underlying pathology of AE, Collard et al (28) compared the plasma biomarker profiles between patients with AE-IPF, acute lung injury and stable IPF. The results indicated a significant increase in the levels of type II alveolar epithelial cell injury/proliferation markers [Krebs von den Lungen-6 (KL-6) and surfactant protein D], endothelial cell injury markers (von Willebrand factor), inflammation markers (interleukin-6) and coagulation markers (protein C, thrombomodulin and PAI-1) in patients with AE-IPF. Kataoka et al (13) detected high levels of D-dimer and thrombomodulin in BAL fluid from patients with AE-IPF. Song et al (3) reported that increased levels of C-reactive protein are a poor prognostic factor for AE-IPF. These studies suggested that dysfunction of endothelial cells, coagulation abnormalities and inflammation have an important role in the pathophysiology of AE-IPF.

The dual anticoagulant and antiinflammatory action of rhTM has been utilized in the management of AE-IPF (13). rhTM activates protein C by the formation of reversible complexes with thrombin. These complexes inactivate coagulation factors, thereby downregulating intravascular coagulation (23). Inflammation is also suppressed by inhibition of neutrophil adhesion, improved endothelial barrier function, decreased complement activation and expression of inflammatory cytokines, inactivation of bradykinin C3a and C5a and increased high-mobility group box-1 degradation (12,29).

Following a systematic literature search, six unique studies evaluating the efficacy and safety of rhTM in AE-IPF were identified. The dose of rhTM was the same across studies (0.06 mg/kg/day is equivalent to 380 U/kg/day) (30). All studies utilized a 6-day drug protocol with the exception of one study (14), in which the drug was administered for seven days. With the limited evidence, the difference between the 6- and 7-day rhTM protocol remains to be determined. After pooling the data of 145 patients in the study group and 146 patients in the control group, the present results indicated that administration of rhTM decreased the 90-day mortality by 71% (CI, 51-83%) compared with that in patients who were not treated with the drug. Similarly, the 28-day mortality was reduced by 75% (CI, 23-92%) with the administration of rhTM, albeit with a large CI, probably due to the small number of studies with limited sample size included in the

present analysis. The results of the present study are similar to a recently published meta-analysis of Kamiya *et al* (31). In their analysis of four studies, the authors noted a statistical significant difference in 90 day mortality with the use of rhTM in AE-IPF. However, due to fewer studies, no meta-analysis was conducted for 28 day mortality in their study.

The survival rate in the control arm of the present analysis was similar to that in studies utilizing only corticosteroid therapy for the management of AE-IPF (3,4). It is important to note that to date, no randomized controlled trial (RCT) has been performed and the present review is a pooled analysis of non-randomized studies. The absence of randomization potentially introduces bias due to the presence of confounding factors. Mortality in AE-IPF may be dependent on several confounding factors, including disease severity, oxygen partial pressure/fraction of inspired oxygen ratio, D-dimer and KL-6 levels, high-resolution computed tomography (HRCT) pattern (diffuse/non-diffuse) and use of concomitant therapies, including anticoagulants and immunosuppressants (3,4). While multivariate regression analysis performed in the clinical trials by Arai *et al* (23) and Sakamoto *et al* (22) indicated that rhTM independently improved the 90-day survival in patients with AE-IPF, the absence of robust RCTs diminishes the overall level of evidence.

Data from the post-marketing surveillance of rhTM therapy in patients with DIC demonstrated an incidence of all adverse events of 7.1%, with bleeding and serious bleeding complication rates of 5.5 and 6.8%, respectively (32). With similar rates of adverse events in the study (8.8%) and control groups (10%), the present results indicated rhTM to be safe in the management of AE-IPF. None of the included studies reported any serious bleeding events during the treatment with rhTM.

The following limitations should be considered when interpreting the results of the present review. First, as mentioned above, no RCTs were available for inclusion in the present review. The majority of the included studies used a historical control group for which the diagnosis and treatment protocols would have differed. In spite of the authors reporting baseline similarity amongst the study groups, certain confounding factors may have introduced bias in the overall results. Furthermore, the inherent limitations of included studies, e.g. methodological variation, limited sample size and differences in the use of adjunctive therapies, including anticoagulants, immunosuppressants, antibiotics and high-flow oxygen, may have led to skewed results. As another limitation, BAL and HRCT were not rigorously utilized for diagnostic purposes in all studies included. In addition, the difference in general supportive care amongst studies, as well as between the experimental and control groups, may have influenced the results. In addition, it was not possible to pool data other than those of mortality and adverse events in the present meta-analysis. The lack of evaluation of other clinical outcomes in the included studies restricted the present meta-analysis to these variables only. Finally, all studies were reported from a single country. The influence of the region and ethnicity on clinical outcomes requires to be considered.

In conclusion, bearing in mind the limitations our systematic review and meta-analysis, our results indicated that rhTM may improve the short-term mortality in patients with AE-IPF. The drug appears to be safe without any enhanced risk of adverse events. There is a requirement for high-quality RCTs with a large sample size to provide robust evidence supporting its use.

Authors' contributions

BW conceived and designed the study. BW and TL collected the data and performed the literature search. BW was involved in the writing of the manuscript. All authors read and approved the final manuscript.

Ethical approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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