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Review

Can antiviral drugs address the treatment challenges of severe fever with thrombocytopenia syndrome? - a systematic meta-analysis

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Abstract

Background: Severe Fever with Thrombocytopenia Syndrome (SFTS) is an emerging infectious disease with high mortality and severity rates. However, there is no clear treatment plan, specific effective antiviral drugs, or effective vaccine for SFTS. Recent studies have shown that the therapeutic effect of Ribavirin and other commonly used antiviral drugs such as Favipiravir (T-705), on SFTS is still controversial. This meta-analysis was conducted to evaluate the therapeutic efficacy of antiviral drugs on SFTS.

Methods: Relevant studies were searched from Cochrane Library, Web of Science, Embase. and PubMed from inception to June 30, 2022, and updated to 2023. The study screening, data extraction, and quality assessment were conducted by re-searchers independently. A counterpart assessment tool was used to assess methodological quality, and the Stata15 software was employed to perform meta-analysis.

Results: The meta-analysis included 8 studies consisting of 4692 patients. The results showed no significant difference in the mortality rate of SFTS patients between the antiviral drug group and the control group (HR: 0.85, 95% CI: 0.46–1.59, p = 0.618). Antiviral drugs had no noticeable effect on this disease (RR: 0.93, 95% CI: 0.58–1.48, p = 0.747).

Conclusions: At present, antiviral drugs (Ribavirin and Favipiravir) used routinely in clinics show no positive effect on the treatment of SFTS yet and fail to reduce the mortality rate. On the other hand, clinical studies specifically evaluating viral load found that antiviral drugs were effective in the treatment of SFTS patients with low viral load, but the efficacy was not statistically significant.

Key words: SFTS; ribavirin; antiviral; meta-analysis; favipiravir (T-705).

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Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an infectious disease caused by the infection of the novel Bunyavirus, a virus isolated and confirmed from ticks in the area where SFTS cases were found by the Chinese Center for Disease Control and Prevention in 2010. This new Bunyavirus belongs to the genus Phlebovirus of the family Bunyaviridae and is highly sporadic in the mountainous and hilly rural areas of China, South Korea, and Japan [1]. The onset season is spring and summer (May to August), which coincides with the active time of ticks. Haemaphysalis longicornis is the main known vector [2], and there is no established human-to-human transmission of this virus [3]. The clinical symptoms of SFTS include fever, gastrointestinal symptoms, and regional lymph node enlargement. Laboratory tests show thrombocytopenia and leukopenia. Most patients develop multiple organ failures [2,4,5]. Choi *et al.* found that white blood cell count decreased to the lowest within a median of 7 days (IQR: 5-8) and platelet count decreased to the lowest within a median of 8 days (IQR: 5-10) [6]. As an emerging infectious disease, SFTS has a high mortality rate, approximately 6-30% in China [2,7,8], 46 % in South Korea [9,10], and 31-55% in Japan [10,11]. In addition to the detection rate of diseases, age, neurological symptoms, bleeding status, and platelet count were associated with the mortality rate in SFTS.

SFTS is an emerging infectious disease with high mortality and severity rates. Although it is listed as a disease requiring urgent research and development by the World Health Organization [12], to date no standard treatment has been established against SFTSV infection, and no effective SFTS treatment drugs have been determined [3,10,13,14]. There are no commercially available vaccines or chemical agents for the prevention of SFTSV [4,15,16] and no recognized academic guidelines for the treatment of the disease [17]. Therefore, the existing antiviral drugs, such as Ribavirin and Favipiravir, are generally used for clinical treatment.

The currently used antiviral drugs are controversial in

clinical practice. Although Ribavirin can inhibit viral replication in vitro [18,19], its clinical efficacy is not significant. Zhang et al. found that patients who received Ribavirin < 5 days from the onset had lower mortality rates than patients who received Ribavirin ≥ 5 days [20]. Weiliu et al. believed that Ribavirin treatment did not affect platelet count and viral load reduction [21]. Shimojima et al. found that the combination of interferon and ribavirin significantly reduced SFTS virus infection [22]. Favipiravir is a new antiviral drug for SFTS, which has been shown to exhibit strong inhibitory activity against a broad spectrum of RNA viruses in vitro or in animal models [23,24]. The efficacy and safety of Favipiravir (T-705) for the treatment of SFTS are still in clinical trials [25,26]. However, there are currently no recognized standard guidelines for the treatment of SFTS. As of 2022, antiviral drugs such as ribavirin and Favipiravir (T-705) continue to be used clinically as an important measure against SFTS viral infections. Therefore, it is necessary to systematically study the effect of antiviral drugs on SFTS to provide comprehensive information for clinicians to make correct decisions. This study aims to evaluate the efficacy and safety of antiviral drugs in the treatment of SFTS through a meta-analysis of evidence-based medicine.

Methods

Registration

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) statement [27]. The study protocol was registered on PROSPERO successfully (#CRD42022375663).

Literature collection

We searched the literature published in Cochrane Library, web of Science, Embase, and PubMed from inception to June 30, 2022, with the following medical subject headings (MeSH) and keywords including severe fever with thrombocytopenia syndrome, SFTS, Ribavirin, antiviral, etc.

Inclusion and exclusion criteria

The inclusion criteria of eligible studies/literature were as follows: (1) The patient was diagnosed as SFTS by reverse transcriptase polymerase chain reaction (RT-PCR) (or supplemented by other means); (2) One or more antiviral drugs were used in the treatment of SFTS. The exclusion criteria were as follows: (1) Review; (2) Repeated article; (3) Animal experiment; (4) Data extraction cannot be combined with other literature.

Data extraction

Two researchers (SLM and SWY) independently conducted a comprehensive literature search to screen relevant full articles after de-duplication and read the full text after excluding the inconsistent literature to determine whether the study could be included. In case of disagreement, the third person (HMF) participated in discussions and decisions.

The two researchers (SLM and SWY) independently extracted and cross-checked the data using standardized tables, and the disputed articles were referred to a third researcher (HMF) for consensus resolution.

The authors used a standardized data extraction form containing the following items: first author, year of publication, country of residence, patient age, sample size, use of antiviral drugs, supportive treatment, the effectiveness of antiviral use, and survival rate.

Quality assessment

The two researchers (SLM and SWY) assessed the risk of bias in the selected studies independently using the Cochrane Collaboration Risk of Bias Tool (CCRBT) [28,29] and Newcastle Ottawa Scale (NOS) [30]. The methodological quality of potential studies was evaluated according to CCRBT with 7 items designed in the following 6 aspects: (1) Selection bias(Random sequence generation, Allocation concealment), (2) Performance bias (Blinding of participants and personnel), (3) Detection bias (Blinding of outcome assessment), (4) Attrition bias (Incomplete outcome data), (5) Reporting bias (Selective reporting), (6) Other bias. For each entry, "high risk", "low risk" and "unclear" were taken as the bias risk assessment results. JBI mainly evaluated quality from 10 questions, which correspond to 0-2 points from not meeting the requirements to the comprehensive and correct description. A score above 14 was considered to be a low risk of bias. NOS mainly conducted quality assessment from 8 questions in 3 domains, with a full score of 2 points for comparability and 1 point for the remaining seven questions. Studies with a score of 7 to 9 were considered to be of high quality, whereas studies with a score of 4 to 7 were defined as of moderate quality. Assessments were cross-checked by two investigators, and the difference in point of view was resolved by consulting the third investigator (HMF).

Statistical analysis

Stata15.0 software was used for data analysis, and the heterogeneity was quantified by Cochran's Q test and Higgins I2. A $p < 0.10$ or $I^2 > 50\%$ indicated significant heterogeneity in the literature, hence a random effect

model was adopted. Otherwise, the fixed effect model was adopted. When there was excessive heterogeneity, sensitivity analysis, and subgroup analysis were used to explore the source of heterogeneity. Funnel plots were used to visually reflect the publication bias, and Egger and Begg tests were used to conduct statistical tests for publication bias. When publication bias existed, the impact of publication bias on the results of meta-analysis was analyzed by the Trim-and-fill method. A *p* value less than 0.05 was considered statistically significant [31,32].

Results

Literature search results

We obtained 374 relevant literatures from 2011 to 2022 through various major literature data retrieval platforms, including 86 from PubMed, 149 from Embase, 23 from Cochrane, and 116 from Web of Science. Through inclusion and exclusion criteria, 12 articles were included in the meta-analysis (Figure 1). All 12 articles discussed the effectiveness of antiviral drugs for SFTS.

The characteristics of the study

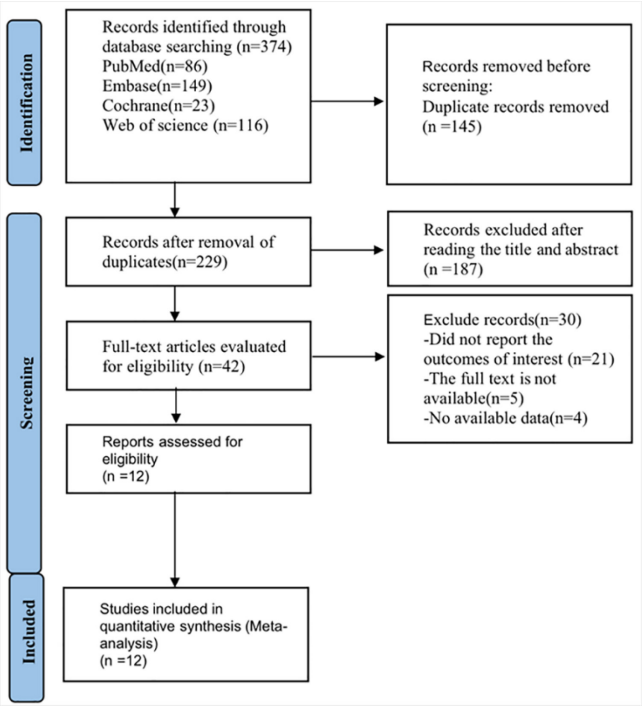
As shown in Table 1, according to the inclusion and exclusion criteria, among all the obtained literature, 8 studies used Ribavirin as an antiviral drug in the obtained literature; 3 articles used Favipiravit (T-705); 1 study on steroids combined with ribavirin treatment. There were 8 articles from China, 1 from Japan, 2 from South Korea, and 1 from Sino-US cooperation. The time and region of the study were consistent with the epidemic and morbidity characteristics of the disease, and there were no significant differences in mean age and gender. All the included quantitative analysis studies were published between 2013 and 2021:1 in 2013 [21], 1 in 2014 [33], 2 in 2015 [9,34], 1 in 2018 [35,36], and 3 in 2021 [20,37,38]. Five China/Asia-based studies were conducted in China [20,21,33-36], one study was conducted in collaboration between

Table 1. Main characteristics of the studies included in the meta-analysis.

First Author	Yr.	Country	Research Type	Age (Yrs.)	Sample size (n[#])	Antiviral drug	No. of days on antivirals	Supportive Therapy	Outcome	Quality Assessment
Yang Yuan	2021	China	RCT	< 60; 60-70; > 70	780 (390/390)	Favipiravir	Median 4-5	No Obvious Explanation	Effective	-
Qing-Bin Lu	2015	China	Cohort Study		574 (408/166)	Ribavirin	3-12	No Obvious Explanation	Ineffective	7
Yibin Lu	2018	China	Cohort Study	Survival Group: 52.3 ± 7.8; Death Group: 66.5 ± 8.9	166	Ribavirin		RHG-CSF; Ulinastatin; Immunoglobulin	Not Mentioned	7
Wei Liu	2013	China	Cross-Sectional Study	61 (7-87)	302 (138/264)	Ribavirin		Doxycycline	Ineffective	19
Koichiro SuemoriI	2021	Japan	Cohort Study	71 (42-91)	26	Favipiravir	7–14	No Obvious Explanation	Effective	7
Sook In Jung	2020	Korea	Cohort Study	Median 68.5	142 (58/83)	steroid	4.5 (3-7.5)	Combined with Ribavirin, plasma exchange, and γ globulin	Ineffective	7
Zhong-Tao Gai	2012	China	Cohort Study	61 (40-83)	59 (All patients)	Ribavirin		No Obvious Explanation	Ineffective	7
Hao Li	2021	China/USA	RCT	(64.7 ± 12.1 vs. 62.4 ± 12.4)	145 (74/71)	Favipiravir (T-705)		No Obvious Explanation	Effective	-
Hao Li	2018	China	Cohort Study	61.4 (SD 12·2)	2096 (478/925)	Ribavirin	> 2	Supportive Therapy	Effective	8
Jaeseung Shin	2015	Korea	Cohort Study	69 (28-84)	35 (9/26)	Ribavirin		No Obvious Explanation	Ineffective	7
Ning Cui	2014	China	Cohort Study	61 (7-87)	357 (194/163)	Ribavirin		Doxycycline	Ineffective	7
Yin Zhang	2021	China	Cohort Study	59 ± 15 (3-84)	62 (40/12)	Ribavirin		No Obvious Explanation	Ineffective	7

[#]n= using antiviral drugs/not using antiviral drugs.

Figure 1. PRISMA flow diagram for screening of eligible studies included in the meta-analysis.

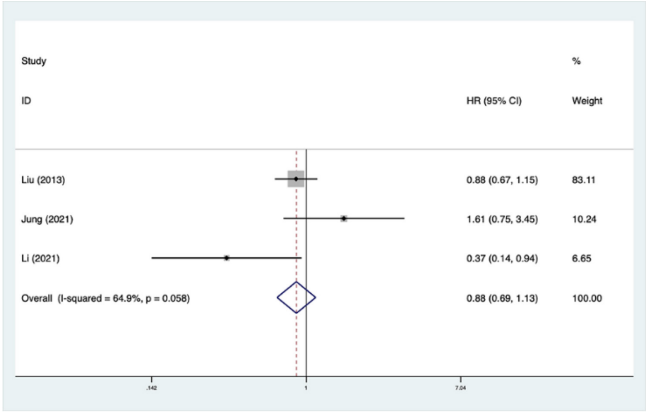


China and the United States [38], and two studies were conducted in South Korea [9,37]. Among the included studies, the sample size was from 35 to 2096. Patients ranged in age from 7 to 87 years old, and the duration of drug use ranged from 1 to 14 days. 1 study that included 2,096 patients had a prospective design embedded in its clinical trial [35,36]; Five studies (1278 patients included) had a retrospective design, and the study of F-705 was a randomized controlled study [38]. For co-stimulators, Ribavirin was used in 6 studies [9,20,33-37], F-705 was used in 1 study [38] and Ribavirin and steroids were used combined in 1 study [37]. 4 studies (2445 patients included) reported survival after the use of antiviral drugs [21,35-38]. Among them, Li *et al.* (2096 patients included) reported data on the use of antiviral drugs by SFTS with low viral loads.

Quality Assessment of included studies

We used the Cochrane Collaboration Risk of Bias Tool (CCRBT) to assess the risk of the included randomized controlled trials (RCTs) studies. As shown in Table 2, researchers presented the risk ratings in seven aspects.

Figure 2. Forest plot of the effect of antiviral drugs (Ribavirin, Favipiravir) on mortality in SFTS.



In the studies of Yuan *et al.* [26] and Li *et al.* [38], patients were aware of the drugs used, so the Allocation consideration was high risk. Other sources of bias were not specified in any of the studies, so other was rated as unclear. The remaining included observational studies were assessed by NOS and JBI, and the risk assessment result is shown in Table 1. None of the studies included in this meta-analysis had a high risk of bias.

Meta-analysis results

Effect of Antiviral Drugs on the Mortality Rate of SFTS

Three studies that did not differentiate viral load reported the mortality data of patients after the use of antiviral drugs. Two studies analyzed the survival rate of SFTS patients with low viral load after the use of antiviral drugs. A random-effects model was adopted to analyze the data, as shown in Figure 2 (I-squared = 64.9%) and (I-squared = 81.2%), respectively). The results showed no significant difference in the mortality rate of SFTS patients between the antiviral drug group and the control group (HR: 0.85, 95% CI: 0.46–1.59, p = 0.618). The analysis on the low level of SFTS viral load also showed no significant difference in the mortality rate of SFTS patients (HR: 1.63, 95% CI: 0.04–61.07, p = 0.792).

Effects of Antiviral Drugs Use on SFTS

Six studies evaluated the improvement of disease after using antiviral drugs. The random-effects model was employed to analyze the data, as shown in Figure 3 (I-squared = 56.1%). The results showed that the use of antiviral drugs had no significant efficacy for the

Table 2. Quality assessment details of included RCTs.

No.	Author	Year	V1	V2	V3	V4	V5	V6	V7
1	Yang Yuan	2021	Low	Unclear	Low	Low	Low	Low	Unclear
2	Hao Li	2021	Low	Unclear	Low	Low	Low	Low	Unclear

V1: Random sequence generation; V2: Allocation concealment, V3: Performance, V4: Blinding of participants and personnel, Blinding of outcome assessment, V5: Incomplete outcome data, V6: Selective reporting, V7: Other bias.

disease (RR: 0.93, 95% CI: 0.58–1.48, $p = 0.747$).
In addition, subgroup analysis was conducted based on the overall and low levels of SFTS viral load, respectively. Antiviral drugs were effective in patients with low SFTS viral load, indicating that SFTS virus load might be a source of heterogeneity. However, there was no statistical difference in the efficacy of Ribavirin in the overall SFTS viral load group (Figure 4).

Sensitivity analysis

By eliminating the literature one by one, the sensitivity analysis on the effect of antiviral drugs on SFTS was performed. The results showed that the circles representing each study were within two boundary lines, indicating the conclusions of this meta-analysis were stable and reliable (Figure 5).

Figure 3. Forest plot of meta-analysis on the effectiveness of antiviral drugs in SFTS patients.

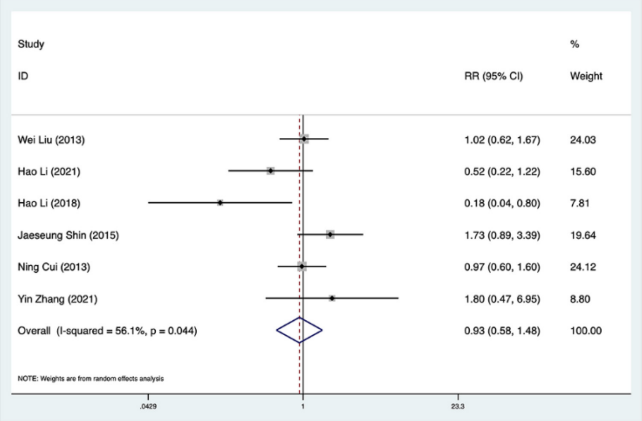
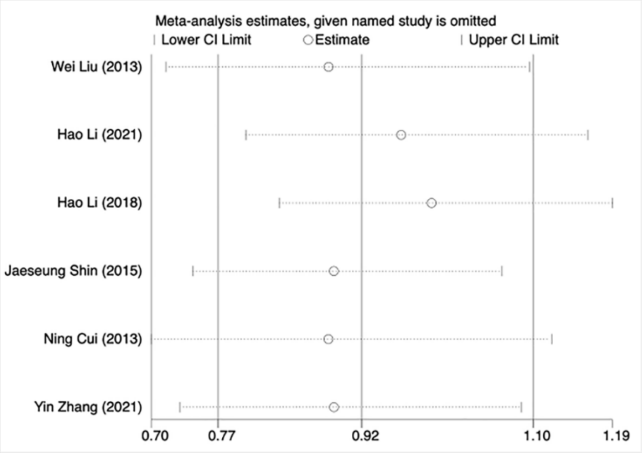


Figure 5. The sensitivity analysis on effect of antiviral drugs in SFTS patients.



Publication bias

We used funnel plots to visually present the publication bias of the effect of antiviral drugs on SFTS, and there was no evidence of publication bias by inspection of the funnel plot and statistical tests (Begg's p = 1.000, Egger's p = 0.955) (Figure 6).

Discussion

This meta-analysis aims to evaluate the efficacy and safety of antiviral drugs in the treatment of SFTS. The results showed that the antiviral drugs (Ribavirin and Favipiravir) mainly applied in clinical practice had no significant effect on improving the cure rate and reducing the mortality rate of SFTS.
Ribavirin is a broad-spectrum antiviral drug with potential effects on a range of DNA and RNA viruses [18,39], and is widely used in clinical practice. It has shown efficacy against many viruses, such as Arenavirus, Hantavirus, and Bunyavirus, and it has

Figure 4. Forest plot of meta-analysis on effectiveness of antiviral drugs in SFTS patients with low viral load.

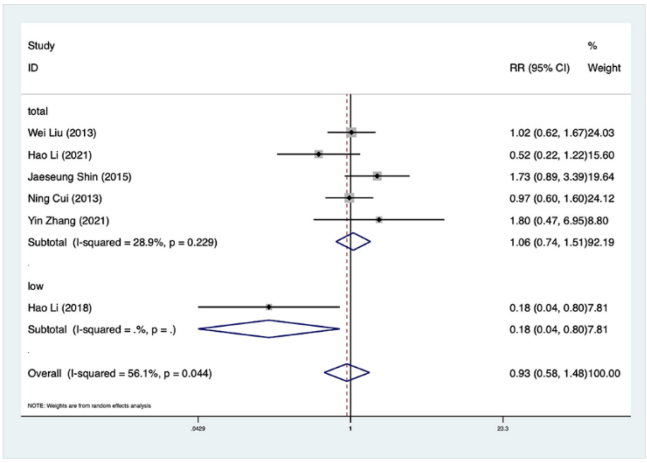
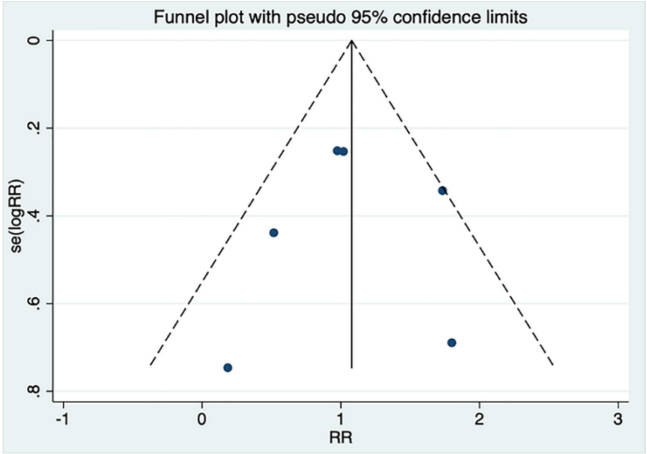


Figure 6. Begg's Funnel plot of publication bias on the effect of antiviral drugs on SFTS.



been confirmed to show good effects on Bunyavirus in vitro [40]. Favipiravir is a selective and potent RNA

polymerase inhibitor of Influenza virus. It is effective for all subtypes and strains of Influenza viruses, as well as other RNA viruses, and is active against a variety of RNA viruses in vivo and in vitro [23,24]. At present, Ribavirin and Favipiravir are the main antiviral drugs used in the treatment of SFTS in clinical practice.

However, this systematic meta-analysis showed that Ribavirin had no positive effect on the clinical manifestations of patients and laboratory indicators, with no significant effect on the treatment of patients.

Although T-705 treatment significantly reduced CFR of patients, those receiving T-705 treatment took less time to clear SFTSV, had fewer signs of bleeding, and showed a faster recovery of neutrophils and lymphocytes, indicating positive therapeutic effects [38,26]. However, Favipiravir showed no significant effect on the treatment of the disease in the meta-analysis of Favipiravir and Ribavirin.

This meta-analysis revealed that antiviral drugs had no statistically significant effect on the mortality rate of SFTS patients. However, when further evaluating the efficacy of Ribavirin based on different SFTS viral loads, Zhang et al. concluded that when the viral load was less than 1 × 106 copies per mL, the survival time was longer in patients receiving Ribavirin than those not receiving Ribavirin. The results suggested the efficacy of Ribavirin in the treatment of SFTS may depend on the level of viral load, and early administration of Ribavirin could be associated with reduced mortality rates of patients. The efficacy of Ribavirin in treating SFTS needs to be further demonstrated. Similarly, according to an RCT of Favipiravir in the treatment of SFTS, the mortality rate of patients who received Favipiravir combined standard treatment decreased by 46.6% compared with those receiving standard treatment alone; in the low viral load group, T-705 could significantly reduce CFR and improve neurological symptoms, which proved that Favipiravir has a positive effect on the survival rate of patients. Yuan et al. also confirmed this in his study [26]. However, this meta-analysis showed that the effect of Favipiravir was still not statistically significant. This may be due to the limited number of the included RCTs and participants.

Based on the analysis of the included data and clinical treatment reports, we found that antiviral drugs can prolong the survival time of SFTS with low viral load, reduce CFR and improve neurological symptoms, which is of positive significance to the treatment of the disease. However, due to the lack of assessment of viral load in clinical practice, few studies focused on antiviral drugs of different concentrations for various viral loads. Besides, the number of relevant RCTs and participants was limited. Thus, no sufficient data are available for statistical analysis, making it statistically impossible to conclude that antiviral drugs had an effect on SFTS with low viral load. Therefore, the efficacy of antiviral drugs in treating SFTS with viral load needs to be further demonstrated.

This meta-analysis has the following strengths. First, it was the first comprehensive statistical analysis of previous studies on the clinical use of antiviral drugs, especially Ribavirin, in the treatment of SFTS, so as to provide a reference for the selection of subsequent clinical treatment regimens. Second, it provided new ideas for future research directions. In clinical practice, where possible, the detection of viral load should be intensified, and the concentration of antiviral drugs may vary for different viral loads. The effect of antiviral drugs in SFTS patients with low viral load and the feasibility of prophylaxis should be further analyzed. More RCTs on Favipiravir (T-705) should be designed to further explore its therapeutic effect on SFTS.

Nonetheless, this study has some limitations as well. Firstly, there were few eligible RCTs of antiviral drugs for SFTS, and most of the included studies were observational studies. Secondly, significant heterogeneity was observed in the results, but, the source of heterogeneity cannot be further explored due to the limited number of the included studies. A larger sample size and the corresponding basic information are needed in the future to allow for the analysis of more variables, such as different regions, races, and ages. Finally, due to the lack of sufficient data on laboratory indicators (inflammation indicators and platelets), further analysis cannot be performed.

Conclusions

In conclusion, the commonly used antiviral drugs have no significant effect on SFTS and may not affect the survival rate. However, as the research on SFTSV is still in its infancy, there is currently no specific drug for the treatment of SFTS. Hence, these commonly used antiviral drugs are still used in clinical practice. Among them, Favipiravir is a promising drug for the treatment of SFTS, but further clinical trials and verification are needed. Only effective antiviral drugs and correct therapies can reduce the mortality rate of SFTS and improve symptoms of SFTS.

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Author contributions

Conceptualization: LMS, MFH, SBL. Data curation: LMS, MFH, SBL. Formal analysis: LMS, JJL. Investigation: LMS, JJL. Methodology: LMS, JJL, SBL. Project administration: LMS, JJL. Software: MFH, WYS, SBL.Supervision: MFH, WYS, SBL.Validation: MFH, WYS, SBL.Writing -original draft: LMS, MFH, JJL, WYS, SBL. Writing-review & editing: LMS, MFH, JJL, WYS, SBL. Ethics approval and consent to participate: Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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