Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Thymosin a1 use is not associated with reduced COVID-19 mortality

Coronavirus disease 2019 (COVID-19) is a global health threatening infectious disease. It causes characteristic inflammatory response, vascular injury, microvascular disease, angiogenesis and extensive thrombosis [1], which can cause acute respiratory distress syndrome (ARDS) and respiratory failure [2]. COVID-19 is characterized by delayed immune reconstitution (IR) and cytokine storm (CS) [3]. In most of the elderly and severe patients with COVID-19 showed high levels of inflammatory cytokines IL-2R, IL-6, IL-10 and TNF-a, and the absolute numbers of T lymphocytes, CD4 + T cells and CD8 + T cells decreased [4].Studies have shown that thymosin a1 can decrease the levels of cytokine expression [5], modulate the immune response homeostasis [6].However, the use of thymosin a1 and COVID-19 have not been determined. The study aimed to analyze the potential association between the use of thymosin a1 and the mortality of COVID-19.

We have systematically searched the databases of Central, EMBASE, PubMed, CNKI, VIP, CBM and Wanfang, using the keywords "thymosin a1" and "COVID-19", until the present time (March 20, 2021).The language was limited to English. The title, abstract and full text of all the articles that met the search criteria were evaluated, and those who reported the use of thymosin a1 in patients with COVID-19 included in the definition of "mortality" are the following Meta-analysis.

The two indexes were expressed by 95% confidence interval (CI), and the binary data were analyzed by relative risk ratio (RR). When p value ≤0.1 and I_2 value >50%, there was significant heterogeneity, so random effect model was used; otherwise, fixed effect model was used.

Through the system electronic retrieval and other ways, a total of 6 studies were obtained. After screening the title, summary and full text, 1498 patients with COVID-19 were included in meta-analysis in four studies [7-10]. Table 1 summarizes the basic features of inclusion studies, and the individual and collective RRs analysis of the relationship between thymosin use and mortality is shown in Fig. 1. Our summary analysis showed that there was no significant correlation between thymosin a1 treatment and mortality [RR 1.24 (95% CI 0.33–4.68), $p = 0.76$, $I^2 = 94\%$].

According to our meta-analysis, there was no significant association between thymosin α 1 treatment and mortality. In the four studies we included, only Sun et al. 's study suggested that there was no significant correlation between thymosin a1 treatment and mortality. The possible reason is that the patients were all critical type patients, nearly half of the patients needed invasive mechanical ventilation, and the total mortality was 52.4.Such complex pathophysiological changes lead to the failure of thymosin a1 to play an effective therapeutic role. Another reason is the lack of sufficient immune related indicators in this study, which makes it difficult to determine the therapeutic effect of thymosin a1 on patients with COVID-19. COVID-19 can lead to immune system dysfunction and poor prognosis. Thymosin a1 is a peptide originally isolated from thymus tissue, which has dual mechanisms during inflammation [7,11]. It can repair T cells by promoting T cell maturation and inhibiting apoptosis, and prevent proinflammatory cytokine storm by increasing regulatory T cells [12-14]. As an immunomodulator, it can regulate the immune response in vivo and specifically inhibit the activation of lymphocytes in CD8 + T cell subsets [15]. Therefore, in a specific group of people, patients with COVID-19 can benefit from thymosin α 1 treatment, such as reducing 28 day mortality and acute lung injury in critically ill patients with COVID-19. We conclude that there is no significant correlation between thymosin α 1 treatment and mortality, but we cannot rule out the beneficial effect of thymosin α 1 treatment on specific patients with COVID-19.

Our article has the following limitations: First, there are few included studies, and studies with no significant association between thymosin treatment and mortality are heavily weighted and may lead to statistical bias. Second, there is little literature on the treatment course and dosage of thymosin α 1 in COVID-19. The effect of thymosin α 1 on COVID-19 needs to be further studied, and large-scale RCT study is expected in the future.

Table 1
Characteristics of included studies

Study	Sample size	Design	Taking thymosin a1 N%	Age(years)	Not taking thymosin a1 N%	Age(years)
Ming Wu et al. [7]	334	Retrospective cohort	102(30.5%)	56.0–69.0	232(69.5%)	40.0–66.2
	771	Retrospective cohort	327(42.4%)	55–71	444(57.6%)	57–74
Yu Wang et al., [8]	317	Retrospective cohort	68(21.5%)	N/A	249(78.5%)	N/A
Yueping Liu et al., [9]	76	Retrospective cohort	36(47.4%)	41.3–69.8	40(52.6%)	53.50–73.75

[1]These authors contributed equally to this work.

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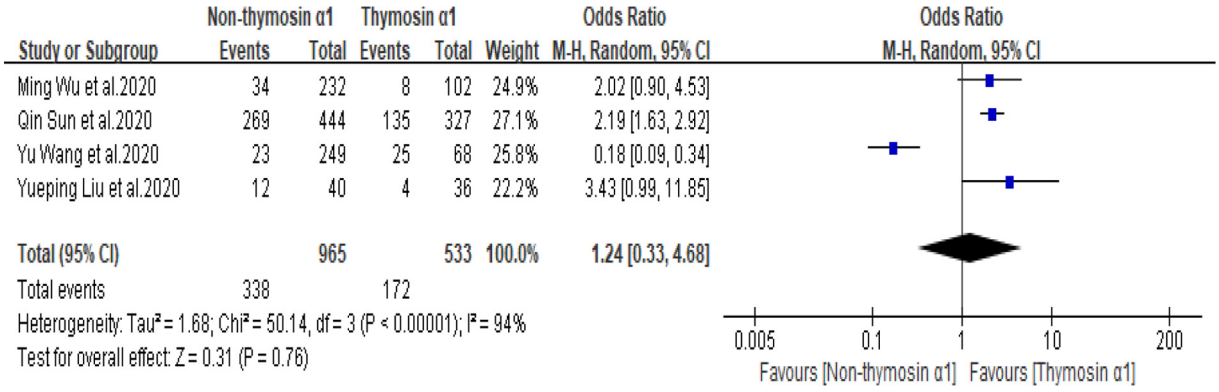

Fig. 1. Forest plot of thymosin a1 associated with mortality from COVID-19.

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Data availability

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

Authors' contributions

All authors contributed to this study. Jingjing Zhang conceived and designed the idea for the study. Tao Liu and Shengdong Liu performed the literature search. Tao Li contributed to the data collection and statistical analysis of the data. Shengdong Liu contributed to the methodological quality analysis. Tao Liu and Shengdong Liu wrote the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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