associated with an increased risk of mortality and prolonged hospital stay compared with AKI caused by other aetiologies. Patients with sepsis and AKI complications have a higher mortality rate than those without AKI.[2,3]

Another important point is that the antibiotic selection for combination therapies in the study was amikacin or colistin in 17/27 (70.8%) of patients. The most widely recognized adverse effects associated with these two antibiotics, which restrict their utilization, is the potential risk of drug-related nephrotoxicity.[4] It is possible that clinicians may have avoided the use of nephrotoxic antibiotics when selecting antibiotics for patients with AKI, which will directly influence the choice of combination therapy. Studies have shown that there are fewer treatment-limiting conditions in patients on combination therapy.[3,5]

Lastly, the pharmacokinetics of antibiotics differ in sepsis patients due to alterations in volume of distribution and antibiotic clearance. Furthermore, the presence of hyperdynamic circulation, fluid balance changes and the development of organ dysfunction, such as AKI, in addition to renal replacement therapy, contribute to a highly complex situation. This situation can vary significantly between patients and even within individual patients over the course of a single day. Therapeutic drug monitoring is recommended to ensure optimal antibiotic dosing in this patient group.[3,6]

In summary, the study presents significant findings regarding combination and monotherapy in patients with *P. aeruginosa* bloodstream infections who developed septic shock. However, for a more comprehensive understanding and interpretation of the study, it is important to consider AKI-related conditions, if any, before antibiotic initiation.

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Transparency declarations

All of the authors declare that they have all participated in the design, execution and analysis of the paper, and that they have approved the final version. Additionally, there are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

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Deleterious effects of a combination therapy using fluoroquinolones and tetracyclines for the treatment of Japanese spotted fever: a retrospective cohort study based on a Japanese hospital database—authors' response

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We appreciate the insightful comments from Itoh *et al*. regarding our study, and we welcome the opportunity to address the key issues raised.

Firstly, we maintain that the term 'deleterious' is appropriate within the context of our study. Our secondary analysis revealed that the mortality rate was significantly higher in the ciprofloxacin combination group. While this finding does not generalize to all fluoroquinolone combination therapies, our primary analysis showed that the adjusted OR (aOR) for mortality in the combination therapy group was relatively high at 2.30 (95% CI: 0.28–18.77) compared with the monotherapy group. Although the wide CI suggests variability, the elevated aOR underscores the need for further investigation into the safety of combination therapies. A similar study by Kutsuna *et al*.[1] reported an OR of 1.94 (95% CI: 0.69–5.43) for in-hospital mortality, which aligns with our findings.

Secondly, Itoh *et al*. raised concerns about convulsions associated with fluoroquinolone or the co-administration of fluoroquinolones and non-steroidal anti-inflammatory drugs (NSAIDs). While our study did not definitively establish a causal link between fluoroquinolone use and convulsions, we reported an observed association between combination therapy and convulsions, particularly when fluoroquinolones were co-administered with NSAIDs. This is a well-known interaction that increases the risk of adverse events and 27.7% of patients in the fluoroquinolone combination group were also prescribed NSAIDs in our study. Combination therapy often leads to the unintentional co-administration of fluoroquinolones and NSAIDs, which presents a non-neglectable risk in real-world settings. It is not solely the fluoroquinolones that cause harm, but the inappropriate drug combinations chosen by physicians, highlighting a broader issue of clinical practice. Therefore, the use of combination therapy demands justification that outweighs the negative aspect of the harmful interaction between fluoroquinolones and NSAIDs. However, the lack of evidence for improved mortality remains a major concern.

We also address Itoh *et al*.'s report of a 0.0% mortality rate (0/39) in their ciprofloxacin group. While this result is noteworthy, we believe it reflects selection bias. Five of 18 cases in the combination group were labelled 'successfully treated', which may not accurately represent the broader clinical context.[2,3] Nationwide data report mortality rates between 1.1% and 4.1%, and Sakabe *et al*. reported a 3.3% mortality rate in fluoroquinolone combination therapy cases.[4,5] The 0.0% rate presented by Itoh *et al*. seems unusually low compared with these benchmarks, weakening their counterargument.

Regarding diagnostic accuracy, we recognize the limitations of using disease codes from the MDV database. However, Japanese spotted fever (JSF) is a notifiable disease under Japanese law, and all cases must be reported and meet strict criteria for reporting to public health authorities. We also excluded suspected cases from our analysis to improve the reliability of our findings.

With respect to fluoroquinolone combination therapy, there is no evidence to support its use for reducing mortality or complications. The only potential benefit reported by Itoh *et al*.[2] is a reduction in fever duration. However, we argue that using fever reduction as an outcome measure is inappropriate.[3] In Itoh *et al*.'s study, more than half of the excluded afebrile cases involved severe conditions such as disseminated intravascular coagulation and/or shock, and all afebrile cases were treated by tetracycline monotherapy. This suggests that severe cases may not always present with fever, making it an unreliable indicator for assessing treatment success. Moreover, combination therapies tend to be reported in cases with a more favourable prognosis, which introduces selection bias and likely accounts for the discrepancies between the interpretation of Itoh *et al*. and our own findings. Importantly, both studies agree that fluoroquinolone combination therapy does not improve key clinical outcomes, such as mortality or complication rates.

As we noted in the limitations section of our manuscript, adjusting for confounding factors remains a challenge in diagnosis procedure combination (DPC)-based studies. JSF is a rare disease, and published case reports on combination therapy often emphasize successful outcomes, while unsuccessful cases are underreported, introducing potential publication bias. This could partly explain the differences in conclusions between our study and that of Itoh *et al*. However, it is important to note that no study, including those conducted by Itoh *et al*., has provided evidence that fluoroquinolone combination therapy improves critical outcomes such as mortality or complication rates.

In conclusion, we stand by our assertion that the inappropriate use of fluoroquinolone combination therapy, particularly when combined with NSAIDs, is associated with deleterious effects. The elevated mortality risk and increased likelihood of convulsions highlight the need for caution when prescribing these drugs. We appreciate Itoh *et al*.'s comments and hope this response clarifies the issues raised and contributes to ongoing discussions on the safe treatment of JSF.

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Transparency declarations

None to declare.

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