Reviewer No. (0058401)

Congratulations for the manuscript. We criticized no comment about the arterial thrombosis in the course of chemotherapy**.**

Thank you for your comment.

Reviewer No. (3017544)

The manuscript entitled “The incidence of venous thromboembolism and the role of D-dimer as predictive marker in patients with advanced gastric cancer receiving chemotherapy: A prospective study” by Kwonoh Park, Baek-YeolRyoo, Min-HeeRyu, Sook Ryun Park, MyoungJoo Kang, JeongHye Kim, Seungbong Han and Yoon-Koo Kang is showing that the incidence of VTE is relatively high in patients with AGC receiving chemotherapy, and pre-treatment D-dimer level might be a biomarker for risk stratification of VTE. Despite their results might be interesting theare some points which need clarification.

Minor points

In abstract section: 1.Are required key-words, no key-definitions

We had described Key words in the previous manuscript, "Advanced gastric cancer; D-dimer; Venous thromboembolism", according to MESH guidelines

In the text and tables:

1.Is not clear pre-treatment therapy, surgical treatment and post-operative mobilization. Clarify it

In the point of prior surgical treatment, 32 patients received a curative intended surgical treatment (please see Table 1). Among them, 18 patients received post-operative adjuvant chemotherapy using TS-1, the others did not receive adjuvant treatment or did not have information about adjuvant treatment due to transfer from other hospital. The current study enrolled patients with advanced gastric cancer such as recurred or initially metastatic, prior treatment including surgical treatment and adjuvant treatment were completed or finished 6 months or more before the enrollment. Because we thought that the readers would not be interested in the descriptions, thus they need not to be explained on manuscript, rather can be explained on this response letter.

2. It would be appropriate to add a table with the clinic-pathological features of patients selected for this study. Alternatively improves Table 1 (ex: tumour site, Lauren Classification).

We added tumor site composed of anatrum/pylorus, body, cardia/fundus, and diffuse pattern in Table 1. We’re afraid that we cannot describe the Lauren classification due to missing data (eg, transfer patients, inappropriate

pathology report)

3. The current study showed the incidence of VTE and role of pre-treatment D-dimer as risk factors in a homogeneous group of AGC patients receiving palliative chemotherapy. In this study, you reported that VTE was not a statistically significant factor for survival, but in Table 1 you reported 21 P/D patients with VTE versus 6 W/D or M/D patients with VTE, and also you reported 18 VTE cases in patients with number of metastatic sites ≥2 versus 9 VTE cases in patients with number of metastatic sites 0-1. Clarify it.

We thank the reviewer for the helpful comment. Patients with histology of poor differentiation or metastatic sites ≥2 were numerically higher in both VTE incidence and time to VTE risk, and poor overall survival compared with those of well or moderate differentiation. However, there was no significant difference of OS between patient with VTE and without VTE. We have added explicit data about the OS in the supplementary table (S1, S2). The reason about these findings might be explained as relatively small number, especially number of VTE development, and poor prognosis of AGC, which made the occurrence of VTE would show less impact on survival duration.

4. Improve Table 4 with second line chemotherapy.

As the reviewer recommended, we have added the information about 2nd-line regimen and 3rd-line regimen in this revised manuscript using supplementary table S3, however, we could not analyze the correlation between chemotherapeutic regimen and VTE, because there were only 9 patients (33%) in 2nd line over excluding 18 patients who developed VTE during treating 1st line chemotherapy.

5. These data are preliminary, they need to be confirmed to further awaited studies. Discuss it in Conclusions.

We appreciate the reviewer for the comment. According to the reviewer's recommendation, we have added the explanation into the 5th paragraph in the 'discussion' as follows: "For these reasons, it is obvious that the present study might not be a confirmative, rather preliminary study for hypothesis generation"

Reviewer No. (2941416)

The authors prospectively examined the incidence rates and risk factors of VTE in AGC subjects who underwent chemotherapy. Unfortunately, the analysis failed to discover any definite predictive factors for VTE. I have some questions and comments.

1. D-dimer levels are associated with liver disease, malignancies and inflammation. Were other inflammatory markers beside WBC count (such as CRP, ESR) checked for inflammation? Did any of the subjects with abnormal D-dimer levels have infections such as UTI or pneumonia which may have confounded the results? The authors should consider checking this.

We agree with the reviewer's point. We checked WBC, CRP among inflammatory markers along with baseline D-dimer. We analyzed the correlation between this inflammatory marker and D-dimer level using Spearman correlation methods, baseline CRP and baseline WBC were correlated with baseline D-dimer such as CRP (Spearman 0.535, P <0.001) and WBC (Spearman 0.256, P < 0.001). We described the correlation between baseline D-dimer and other baseline variables in supplementary table 4. However, baseline WBC and CRP were not significant risk factors for VTE not only in univariate analysis (table 1) but also in multivariate analysis (table 3).Additionally, the current study prospectively enrolled the patients, who were suitable to cytotoxic chemotherapy (eg, excluded patient with active infection), additionally baseline lab including D-dimer were checked within a week before starting chemotherapy (mean: 1.83 ± 2.99 days). Thus, we thought that it would have low possibility that other clinical infectious status came into D-dimer level as cofounding factor.

2. Was there a reason that the authors chose time-to VTE instead of VTE incidence in the statistical analysis? Though they may not be statistically different, the authors should state why they chose such a method of investigating VTE, when the presence of VTE may have been more simple and sufficient.

We appreciate the reviewer for the thoughtful comment. As the reviewer commented, incidence of VTE is simple and easy to understand for the readers, while it would be less informative because it represents all VTE development equally from 1st line setting to terminal status. We thought that early developed VTE (1st line or 2nd line chemotherapy setting) were different from delayed VTE in terms of clinical significance, thus, we used 'time to VTE' instead of 'incidence of VTE'. We have added this explanation into the 'statistical analysis' of Material and Methods section."For risk factor analysis of VTE, we used time to VTE to discriminate early versus delayed development considering the different clinical significance."

3. What were the outcomes of VTE treatment. Though the authors state that there were no significant differences brought on OS by VTE, the readers may be interested in the clinical outcomes of VTE (i.e. Were they successfully treated? The symptoms subsided or not? Differences in quality of life?, etc.) This may suggest ways to successfully treat VTE in AGC patients.

We apologize for the lack of information about the detailed outcome. In spite of the reviewer's recommendation, we could not assess level of symptom relieving and QoL after VTE. We have no remedy to assess the recovery, however, we supposed the recovery that is proper to receive chemotherapy based on the fact that there was no VTE-related death, no permanent discontinuation of chemotherapy, although 10 patients (37.1%) temporally discontinued due to VTE (table 2).

4. Though the authors stated that they did not serially follow D-dimer levels, D-dimer has been primarily used to rule out VTE. As such, I believe that the authors may have checked D-dimer levels when VTE was suspected. Did these levels indeed show an increase compared to the baseline levels? Also, were there differences in the D-dimer levels of subjects with symptomatic or asymptomatic VTE after VTE was detected? Based on this, would a serial follow-up have detected VTE before symptomatic VTE occurred?

We appreciate for your comments. We additionally analyze the correlation of 'baseline D-dimer' and 'D-dimer at the time of VTE' among patients with VTE (n=27) (table 4 in the revised manuscript). D-dimer levels were increased significantly in patients with symptomatic VTE (P = 0.004), on the other hand, those in patients with incidental VTE showed only numerical increase (P = 0.198). Although it is not conformative findings because there was only numerical increase of D-dimer in incidental VTE and no information about the alteration of D-dimer levels in other patients without VTE; these findings imply a hypothesis generation that serial D-dimer evaluations might be valuable to detect VTE.

We added 'table 4' and it's explanation in the 'results' and the interpretation in the 'discussion' as follows;

"Considering that the current study showed that D-dimer level at the time of VTE development is significantly increased compared with that at baseline in patients with VTE, serial measurements of D-dimer might detect early changes and predict the development of VTE."

Table 4 Comparisons of D-dimer levels between baseline and time of VTE development

	Total (*n* = 27)	**Symptomatic VTE** (*n* = 13)	**Incidental VTE** (*n* = 14)	***P* value**
Baseline D-dimer	4.19	3.62	4.72	0.835
D-dimer at the time of VTE development	11.18	14.11	8.45	0.436
	P value	P value	P value	
	0.004	0.010	0.198	

Reviewer No. (48205)12/20

Dear authors Thank you very much for submitting this interesting draft. In this prospective study using a total of 241 patients, authors demonstrated a relatively high incidence and a risk of venous thromboembolism (VTE) in patients with advanced gastric cancer (AGC) receiving chemotherapy and proposed that pretreatment D-dimer level might be a biomarker for risk stratification of VTE. This study provided clinically useful information of the usefulness of D-dimer in predicting the occurrence of VTE during a median follow-up duration of 10.8 months after the chemotherapy. However, there remain some issue, as follows.

Major:

1) Previous studies suggested that smoking and alcohol abuse might be associated with risk of cardio-vascular disorder, so please demonstrate whether these factors can be related to the VTE risk.

In spite of the referee's concern, we are afraid that we did not check the information about smoking and alcohol abuse, rather, we checked existence of cardio-vascular disorders in all participants, and only 4 patients reported cardio-vascular disease histories. Thus, we couldn't further analyze the association between VTE and cardio-vascular disorders due to small number.

2) This cohort was focused on patients suffering from advanced GCs, which can cause upper-GI bleeding, followed by dehydration or severe anemia required for blood transfusion treatment. These phenomena may result in the occurrence of VTE. So, please demonstrate whether symptom of GI-bleeding and blood transfusion treatment can related to the VTE risk.

We apologize for the lack of information about the detailed information about the incidence and intensity of GI-bleeding, blood transfusion, dehydration, and severe anemia were lacking, thus we couldn't demonstrate relationship between GI-bleeding (and/or blood transfusion) and VTE risk.

Minor:

1) There seemed to be mistype in the text, such as VETE in the introduction section.

We thank the reviewer for the helpful comment. We have changed the typo and carefully rechecked other errors.

2) Please change the number of a vertical axis of Figure 1 and Figure 2, from 0~1.0 to 0~100 in one-to-one correspondence to the unit (%).

Thank you for pointing out the errors. We change both Figure 1 and 2 according to the reviewer's recommendation.

3) Considering about the relationship between D-dimer and VTE, the pretreatment D-dimer can be originated from microvascular disorder in the existing gastric tumor. If so, high level of the pretreatment D-dimer may indicate the existence of micro-thrombosis prior to chemotherapy, not the predictor of post-chemotherapy VTE. It will be better for authors to discuss this point. Additionally, from the point of view of the above, I wonder if there may be the relationship between the value of serum CRP and the VTE occurrence after the chemotherapy. Please discuss this point, too.

To some aspects, we agree with the reviewer's point that the VTE might already have been developed at the time of the diagnosis of AGC before chemotherapy, regardless of chemotherapy, as the reviewer suspected. With all

due the respect to the reviewer, the assumption can be confirmed in neither prior studies nor the current study. We thought that patients with higher baseline D-dimer level would represent more susceptibility to VTE development after chemotherapy, and readers might not be interested in the additional explanation of the uncertainty.

Reviewer No. (2537353)

The authors investigated the incidence and risk factors of venous thromboembolism (VTE) in patients with advanced gastric cancer (AGC) receiving chemotherapy. They concluded that the incidence of VTE is relatively high in patients with AGC receiving chemotherapy, and pretreatment D-dimer level might be a biomarker for risk stratification of VTE. The study show different negative points:

1) The absence of a serial measurements of D-dimer

As we explained above in response to reviewer (2941416) number 4, we are afraid that we did not check serial D-dimer, thus did not confirm the roles of serial D-dimer evaluations. We thought that it is one of the important limitations of the current study and described the explanation in the discussion section.

2) The not calculation of the proper number of patients, to detect statistically significant differences in other characteristics such as risk factors or survival.

The current study is a simple observation cohort study including consecutive patients without strict prior sample size calculation. Thus, this study is a preliminary study, as mentioned earlier. We described the limitation in discussion part.

3) The manuscript need to reviewed by native speaker because there are numerous english mistakes

Thank you for your comments. We carefully checked the English mistakes again, and now attach the certification of the English translation.