Author's response to reviews

Title: Risk of stroke in patients with ovarian cancer: a nationwide population-based study

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Date: 13 February 2014

Author's response to reviews: see over
February 14, 2014
Sabina Alam, PhD
Claire Barnard, PhD
BMC Medicine
BioMed Central
236 Gray's Inn Road
London WC1X 8HB
United Kingdom


Dear Dr. Sabina Alam and Dr. Claire Barnard,

Thank you for the opportunity to revise and resubmit our manuscript entitled “Risk of stroke in patients with ovarian cancer: a nationwide population-based study.” We are pleased to learn that revision and resubmission of this work have been encouraged. We have revised this manuscript according to each of your and the reviewers’ comments. Following this cover letter is our detailed response to each of the reviewers’ comments. Enclosed, please kindly find one copy of manuscript with changes (highlighted in red) and a clean copy of the revised manuscript with filenames “BMC-Med-8793347111825582-R1-changes.doc” and “BMC-Med-8793347111825582-R1-clean.doc”, respectively. The files of title page and this cover letter “BMC-Med-8793347111825582-R1-reply.doc” also enclosed.

We appreciate the helpful comments from the reviewers and hope that this new revision now meets the high standards of BMC Medicine to be accepted for publication.

Sincerely yours,

Chia-Jen Liu, M.D.
Response to the editor:

General comment:

Regarding referee 1’s comment about the unequal follow-up of the two cohorts, we asked the statistical reviewer to comment on this point specifically. As you can see, the statistical reviewer is satisfied that this analysis has been done appropriately, and has indicated a few minor statistical revisions that need to be made.

Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

REPLY: Thank you for all your kind help. We are pleased to see our manuscript being reviewed by a statistical expert giving us many valuable suggestions. We have revised our manuscript according to these important comments. We have also updated the format of our manuscript according to the journal style of BMC Medicine and hope that this revision would meet the high standard of the Journal.

Specific comment #1:
1. Please include information in the Methods section about the ethical approval and informed consent from the participants in your study. If the need for ethical approval and consent was waived by an ethics committee, a statement to this effect should be included in the Methods section.

REPLY: Thank you for your remind. Since the Taiwan NHI research database contains encrypted computerized data for research purposes, the ethics committee of Taipei Veterans General Hospital informed us, before this study was initiated, that this study was exempted from full review and that each patient's informed consent was not required. We have included statement of ethical approval and informed consent in the Methods section.

Please refer to page 7, lines 117–120:

“Since the Taiwan NHI research database contains encrypted computerized data for research purposes, the ethics committee of Taipei Veterans General Hospital informed us that this study was exempted from full review and that each patient's informed consent was not required.”

Specific comment #2:
2. Authors’ contributions: Please describe the role of TJC and CHT other than “administrative, technical and material support”, and confirm whether all authors approved the final version. Please note that to qualify as an author one should 1) have made substantial contributions to
conception and design, or acquisition of data, or analysis and interpretation of data; 2) have been involved in drafting the manuscript or revising it critically for important intellectual content; 3) have given final approval of the version to be published; and 4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REPLY: Thank you for your remind. We have updated the role of TJC and CHT in the Authors' Contributions section. We have also ensured all authors approved the final version as well as agreed to be accountable for all aspects of the work.

Please refer to page 16, line 314 & lines 318–319:
“ASK, CJT, HHW, TJC, and CHT gave the final interpretation of the results.”
“CJL acts as guarantor and accepts responsibility for the integrity of the work as a whole.
All authors read and approved the final manuscript.”

Specific comment #3:
3. If appropriate, please add an Acknowledgements section to the end of your manuscript to acknowledge anyone who contributed towards the article by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for each author, and for the manuscript preparation.

REPLY: Thank you for your kind remind. We've added an Acknowledgements section in the manuscript.

Please refer to page 16, lines 320–328:
“Acknowledgements
This study is supported in part by a grant from Taipei Veterans General Hospital (V103B-022 and V103E10-001). The supporting sources have no role in the study design or conduct, or in the decision to submit for publication. The study is based on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance (BNHI), Department of Health, Executive Yuan, Taiwan and managed by National Health Research Institutes (NHRI), Taiwan. We express our particular gratitude to the government organization BNHI and the non-profit foundation NHRI.”

Response to reviewer 1:

Major comment #1:
1. The duration of follow-up in the ovarian cancer and control cohorts was very different,
median 2.68 yr for the cancer group and 3.85 yr for the control. This makes for a very unequal comparison. The limitation is the follow-up of the ovarian cancer patients - which is understandable. However, shouldn't the authors have matched the follow-up of the control group to the cancer group as they matched everything else given that longer follow-up of these patients will increase the number of strokes in the control population and reduce the potential effect of the cancer? I think this is the most serious issue and needs to be addressed. They may have grossly underestimated the HR of stroke in the ovarian cancer population.

REPLY: The statistical methods we used (e.g., Cox regression, log rank test) do take into account the different lengths of the two groups, the ovarian cancer population and the matched control population, as agreed by the statistical reviewer (Dr. Peter N Lee). The analysis between 2 cohorts with different follow-up periods could also be seen in many match cohort studies in the oncology fields. For example, long-term cervical cancer survival between laparoscopic versus open radical hysterectomy (median follow-up times, 63 months in laparoscopic surgery group v. 127 months in open surgery group) [1], pregnancy between cancer survivors versus controls (median observation times, 6.2 years in male patients v. 8.2 years in male controls, 5.0 years in female patients v. 6.5 years in female controls) [2].

Since the follow-up periods do not influence the test model with Cox regression and log rank test, we do not test the statistical difference between the two groups. Instead, we described the follow-up duration in the Results section, both in the abstract and full text.

References in the reply:

Please refer to page 4, lines 65–67 & page 10, lines 183–185:
“After a median follow-up of 2.68 and 3.85 years, respectively, the ischemic stroke incidence was 1.38-fold higher in the ovarian cancer cohort than in the comparison cohort (9.4 vs. 6.8/1000 person-years),”
“The median follow-up duration was 2.68 years (IQR 1.44 to 4.98 years) for the ovarian cancer group and 3.85 years (IQR 1.83 to 6.14 years) for the matched cohort group.”

Major comment #2:
1. Several standard vascular risk factors were prominent in the ovarian cancer population such as hypertension, increasing age, etc. However, there is no comment on the effect of these risk factors in the control group. Did they have a similar HR in the control group or was there an
interaction between these standard risk factors and the presence of ovarian cancer, or the use of platinum-based chemotherapy? This is important in trying to understand the mechanisms and tease out whether platinum-based therapies accounted for the majority of the increased risk seen in the ovarian cancer population.

REPLY: We sincerely thank you for the import point of view, which was also mentioned by the statistical reviewer (Dr. Peter N Lee). We performed an analysis on the effect of the risk factors in the control group and found out that age \( \geq 50 \), diabetes mellitus, and hypertension were all significant risk factors for stroke events with hazard ratios (HRs) of 3.89, 1.53, and 2.43 respectively. We believe that the matched control cohort is appropriate and representative. These results resemble that of the ovarian cancer group, in which elderly \( \geq 50 \) years (HR, 2.21), diabetes mellitus (HR, 1.71) and hypertension (HR, 1.84) possess similar risk.

Please refer to Additional table 1 as below:

### Additional table 1 Analyses of risk factors for ischemic stroke in patients without ovarian cancer

<table>
<thead>
<tr>
<th>Predictive variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Age ( \geq 50 )</td>
<td>5.99 (4.25–8.43)</td>
<td>\textless 0.001</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.76 (2.11–3.60)</td>
<td>\textless 0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.39 (3.40–5.67)</td>
<td>\textless 0.001</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1.55 (1.04–2.29)</td>
<td>0.030</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2.11 (1.62–2.74)</td>
<td>\textless 0.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2.87 (1.07–7.71)</td>
<td>0.037</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4.74 (2.11–10.65)</td>
<td>\textless 0.001</td>
</tr>
<tr>
<td>Peripheral arterial occlusive disease</td>
<td>2.54 (0.36–18.13)</td>
<td>0.352</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.

<sup>a</sup> All factors with \( P < 0.1 \) in univariate analyses were included in the Cox multivariate analysis.

In the table 3, we aimed to perform further analysis to clarify significant predictive risk factors for ischemic stroke in ovarian cancer patients. The univariate and multivariate analyses were performed only in ovarian cancer cohort, and the statistical results revealed that platinum-based (e.g., cisplatin- and carboplatin-based) therapy was one of the significant predictive factors. We did not calculated the hazard ratio comparing ovarian cancer cohort and matched control cohort, because platinum-based therapy was not one of the factor during matching process. Consequently, we made the conclusion that age (HR 2.21), hypertension (HR 1.84), diabetes (HR 1.71), and chemotherapy treatment (HR 1.45), especially platinum-based regimens (HR 1.38 for cisplatin-based and 1.46 for carboplatin-based regimens), were independent risk factors of developing ischemic stroke in ovarian cancer patients. Accordingly, it could not be overemphasized whether platinum-based therapies
accounted for the majority of the increased risk seen in the ovarian cancer population; it could only be said that ovarian cancer patients who received platinum-based therapies would possess 1.45-fold risk for ischemic stroke compared with those who did not receive platinum-based therapies.

Please refer to page 5, lines 75–77 in the abstract, and page 11, lines 198–202 and 204–208 in the Results section:

“Conclusions
Ovarian cancer patients were at an increased risk of developing ischemic stroke. Age, hypertension, diabetes, and chemotherapy treatment were independent risk factors.”

“In the multivariate Cox proportion hazards model, risk factors independently determining the subsequent ischemic stroke in ovarian cancer patients included: age ≥ 50 years (HR 2.21; 95% CI 1.64 to 2.99; P < 0.001), diabetes mellitus (HR 1.71; 95% CI 1.27 to 2.29; P < 0.001), hypertension (HR 1.84; 95% CI 1.39 to 2.43; P < 0.001), and chemotherapy treatment (HR 1.45; 95% CI 1.07 to 1.97; P = 0.017) (Table 3)”

“Comparing different chemotherapy modalities, cisplatin- (HR 1.38; 95% CI 1.07 to 1.76; P = 0.012) and carboplatin-based regimens (HR 1.46; 95% CI 1.13 to 1.89; P = 0.004) were independent risk factors for subsequent ischemic stroke, whereas non-platinum–based regimens (HR 1.12; 95% CI 0.61 to 2.04; P = 0.722) were not.”

Minor comment #1:
1. Was thromboembolic disease recorded in the database and could the authors find any association with stroke in the cancer population?

REPLY: Thank you for the important comment. From the Taiwan National Health Insurance Database, we identified two thromboembolic diseases, deep vein thrombosis (DVT) and pulmonary embolism (PE), in ovarian cancer patients to clarify the association. Interestingly, we found out that the incidence DVT was significantly higher in patients with ischemic stroke (7.31% vs. 2.57%, P < 0.001 using chi-square test) while there was no difference for PE. We also analyzed these risk factors, being regarded as time-dependent covariates, with multivariate Cox regression models and found out that DVT, but not PE, would independently correlate subsequent ischemic stroke (HR 2.41; 95% CI 1.49 to 3.90). For these interesting exploratory data, pointed out by your comment, we are planning the next study focus on the vascular episodes, probably including arterial and/or venous thrombotic events, in this particular patient group.

Please refer to Supplemental tables 1 & 2 as below:

Supplemental table 1 The percentage of thromboembolic diseases (deep vein thrombosis and pulmonary embolism) in ovarian cancer patients with and without ischemic stroke

<table>
<thead>
<tr>
<th>Thromboembolic diseases</th>
<th>Patients with ischemic stroke</th>
<th>Patients without ischemic stroke</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Supplemental table 2 Risk factors for ischemic stroke in patients with ovarian cancer

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>3.06 (1.90–4.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0.00 (0.00–*</td>
<td>0.970</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.

*a As a time-dependent covariate in the Cox regression model.

*b Don’t converge.

### Minor comment #2:

2. The other tantalizing piece of information on page 14, line 264 is the suggestion that the increased risk of stroke is present immediately at diagnosis - which can’t be explained by platinum therapy. Do the authors have data on the time when strokes occurred?

**REPLY:** Thank you for the important comment. In our study, patients who had stroke before and at time of diagnosis of ovarian cancer were excluded. During the follow-up period, stroke appeared to occur immediately after ovarian cancer diagnosis in a few patients with a growing disparity of stroke risk between cancer and control cohorts. Indeed there were a few stroke events before platinum therapy. We believe that platinum therapy is one of the risk factors, other than disease *per se* and patients' underlying comorbidities. In the Discussion section, we pointed out this phenomenon; this may serve to inform clinicians to consider close surveillance once ovarian cancer was confirmed.

Please refer to page 14, lines 269–271:

“Our study revealed that ovarian cancer patients appeared to have a higher risk of stroke soon after cancer diagnosis, and the increased risk persisted throughout the follow-up period.”

Accordingly, we would like to show the number and the timing of stroke in the ovarian cancer cohort. Please refer to Supplemental figure 1 as below.

Supplemental figure 1 Histogram for ischemic stroke in patients with ovarian cancer
Discretionary #1:
1. The whole paragraph on RT on page 14 doesn't add anything, and I would delete.

REPLY: Thank you for your kind suggestion. We’ve deleted the whole paragraph on RT, originally in page 14, lines 271–278.

Response to reviewer 2:

Major comments #1:

This is an epidemiologically based paper, demonstrating that patients with ovarian cancer have a higher risk to suffer from stroke. 2 cohorts of app 8000 patients are compared, and age, hypertension, diabetes mellitus and "chemotherapy" seem to increase the precipitating factors which could be identified. Chemotherapy is suggested, that platinum drugs in particular increase the risk to suffer from stroke.

It is an incredibly large sample, which in effect turns out that the risk of stroke for patients with ovary cancer is increased by 1.38. The risk factors as age, hypertension and diabetes are expected, and it seems surprising, that they are prominent in the ovary-cancer group.

REPLY: Thank you for your feedback. We searched on Pubmed about prevalence of diabetes and hypertension in ovarian cancer patients. The prevalence of diabetes in ovarian cancer patients varied among studies of different regions, as low as 2.4–4.9% in Danish cohorts [3-6] and 10–12.9% in US
cohorts [7-9]; both were lower than ours (16.4%). The difference between western and our report might originate from distinct region effect. In our dataset, the accuracy of diabetes diagnosis in health insurance claims data had been validated [10], and the diagnostic accuracy of ovarian cancer is reliable based on the system of Registry for Catastrophic Illness. Thus we believe that the prominent prevalence of diabetes in ovarian cancer patients is trustworthy.

The prevalence of hypertension, as reported by the University of Texas MD Anderson Cancer Center, was as high as 59% [9]. Jørgensen et al. also reported the prevalence of comorbidity, although not specified each, around 45% based on American Association of Anaesthetists (ASA) category 2 risk, which indicates mild systemic disease such as essential hypertension or mild diabetes [11]. Both were much higher than ours (27.5%), and this might be caused by the regional difference. To our knowledge, this is also the first population-based study indicating the prevalence of comorbidities in ovarian cancer patients in Asia, and might reserve as the basis of further epidemiologic studies in the field of gynecologic malignancies.

Since the matched control cohort was also chosen on the basis of comorbidities related to cerebrovascular events (other than age, gender, and time of enrollment), so the prominence of hypertension and diabetes would not influence the result of analysis.

References in the reply:
Major comments #2:

It is the study of a large cohort, and although basic information can be compared, no detail to either stroke type, nor coagulation can be given. This may be of importance, as the issue of stroke type has been discussed extensively in literature, as well as coagulations disorders. The assumption of a disarray in coagulation disorders is carried forward through many years, although the precise type of coagulation disorder, except some types of leukemia has never been defined. D-dimer seems to be changed in some series, but this is not specific.

REPLY: In this study, we aim to investigate the association of ovarian cancer and ischemic stroke using population-based data. Hence, only ischemic stroke was identified from the database as an event among the ovarian cancer and control cohorts. We have to emphasized that the record of ischemic stroke had been validated in Taiwan National Health Insurance Research Database, and the coding was with accurate confirmation [12]. We mention such outcome measures in the Methods section.

References in the reply:


Please refer to page 8, lines 136–138:

“Ischemic stroke identification using data in the Taiwan NHI is highly accurate compared to other insurance databases and is valid for population-based research [9].”

One of the limitations of the National Health Insurance Database in Taiwan is lack of biochemistry profile (e.g., coagulation profile such as prothrombin time, activated partial thromboplastin time, D-dimer, fibrinogen, and fibrin degradation product, etc), which was required for further exploration of coagulation disorder in these patients. Thus, we did not make any conclusion about the correlation between ovarian cancer and coagulation disorders. We included this limitation regarding biochemistry profile in the Discussion section.

Please refer to page 14, lines 277–280:

“This study has several limitations. First, lifestyle variables and behavioral factors, such as tobacco and alcohol use, body mass index, dietary habits and biochemistry profile such as
Although our database lack of these coagulation profiles, we performed analysis, as suggestions from reviewer 1 (Dr. Lisa M. DeAngelis), on two thromboembolic diseases, deep vein thrombosis (DVT) and pulmonary embolism (PE), in ovarian cancer patients to study their association. Interestingly, we found out that the incidence DVT was significantly higher in patients with ischemic stroke (7.31% vs. 2.57%; \( P < 0.001 \) using chi-square test) while there was no difference for PE. We also analyzed these risk factors, being regarded as time-dependent covariates, with multivariate Cox regression models and found out that DVT, but not PE, would independently correlate subsequent ischemic stroke (HR 2.41; 95% CI 1.49 to 3.90).

Please refer to Supplemental tables 1 & 2 as below:

Supplemental table 1 The percentage of thromboembolic diseases (deep vein thrombosis and pulmonary embolism) in ovarian cancer patients with and without ischemic stroke

<table>
<thead>
<tr>
<th>Thromboembolic diseases</th>
<th>Patients with ischemic stroke</th>
<th>Patients without ischemic stroke</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>19</td>
<td>7.31</td>
<td>216</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0</td>
<td>0.00</td>
<td>1</td>
</tr>
</tbody>
</table>

Supplemental table 2 Risk factors for ischemic stroke in patients with ovarian cancer

<table>
<thead>
<tr>
<th>Variables</th>
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<td>0.00 (0.00–*)</td>
<td>0.970</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.

*aAs a time-dependent covariate in the Cox regression model.

Don’t converge.

Major comments #3:

Chemotherapy and stroke is also an interesting issue. The authors at one point speak of chemotherapy (in general), then on "platinum based" drugs. This is also referred to in the tables. It may be worthwhile to explore this further, as the assumption of an increased stroke risk is based on case observations and small series, and would definitely need confirmation in large series. The question appears, whether any other chemotherapies have been used at all.

REPLY: Thank you for your feedback. Initially, we identified chemotherapy as an independent risk
factor for ischemic stroke in the ovarian cancer cohort using multivariate Cox proportion hazards model. Furthermore, we investigated the risks carried by different types of chemotherapy (cisplatin- and carboplatin-based regimens vs. non-platinum–based regimens), and found out that the platinum-based regimens would independently increase subsequent ischemic stroke risk while non-platinum–based regimens would not. In the literature review, we have found many previous reports that may serve as part of explanations. We consider the results as our main findings, and discuss it thoroughly in the Discussion section.

Please refer to page 11, lines 204–208 & page 13, lines 253–268:
“Comparing different chemotherapy modalities, cisplatin- (HR 1.38; 95% CI 1.07 to 1.76; 
P = 0.012) and carboplatin-based regimens (HR 1.46; 95% CI 1.13 to 1.89; P = 0.004) were independent risk factors for subsequent ischemic stroke, whereas non-platinum–based regimens (HR 1.12; 95% CI 0.61 to 2.04; P = 0.722) were not.”

“While the mechanism is still uncertain, some suggested pathophysiologies are associated with increased fibrinopeptide A and decreased fibrinolytic activity [24], elevated plasma von Willebrand factor [25], hypomagnesium-associated vascular spasm [26, 27], endothelial injury [28, 29], and mononuclear cell-mediated platelet activation [30]. Moreover, Li et al. demonstrated that platinum in chemotherapy regimen, which is also commonly used for treating ovarian cancer patients, may increase the risk of ischemic stroke among the cancer patients [31]. Cerebral infarction after cisplatin-based chemotherapy in ovarian cancer patients was reported previously [32, 33]. A meta-analysis of 38 randomized phase II and III trials showed that cancer patients who received cisplatin-based chemotherapy demonstrated a dose-dependently increased risk (RR 1.67, 95% CI 1.25 to 2.23; P = 0.01) of thromboembolism compared to patients who received a non-cisplatin–based regimen [34]. More research is needed to clarify the role of chemotherapy in the relationship of ovarian cancer and subsequent ischemic stroke, as well as to determine whether it is necessary to use a prophylactic antiplatelet agent in high-risk patients during the chemotherapy period.”

Major comments #4:
In summary, looking at the time perspective of this study, this is an analysis of the appearance of stroke, after diagnosis and treatment in a given, defined disease. It differs from other approaches, where stroke at presentation, during treatment and possibly to specific cancer mechanisms have been made. It also differs from the retrospective study by Graus et al, who were able to examine the pathological results. This study was from one center, and based on the pathological endpoint.

Despite the shortcomings, which may be important to follow, this is an interesting observation. The paper should be overworked, some parts of the discussions shortened to the
facts appearing in the study, and also the role of chemotherapy explained, as well as possible metastatic sequelae to the brain.

**REPLY:** Thank you for your important suggestions. We have removed the part on radiotherapy (originally in page 14, line 271-278) in the Discussion section and made it more focused on the facts appearing in this study. For example, we had performed a brief summary on findings of previous studies about the role of chemotherapy and the timing of stroke events after ovarian cancer diagnosis.

Please refer to page 13, lines 253–259 and page 14, lines 269–272:

“While the mechanism is still uncertain, some suggested pathophysiology are associated with increased fibrinopeptide A and decreased fibrinolytic activity [24], elevated plasma von Willebrand factor [25], hypomagnesium-associated vascular spasm [26, 27], endothelial injury [28, 29], and mononuclear cell-mediated platelet activation [30]. Moreover, Li et al. demonstrated that platinum in chemotherapy regimen, which is also commonly used for treating ovarian cancer patients, may increase the risk of ischemic stroke among the cancer patients [31].”

“Our study revealed that ovarian cancer patients appeared to have a higher risk of stroke soon after cancer diagnosis, and the increased risk persisted throughout the follow-up period. A similar phenomenon was also observed in head-and-neck cancer [19, 21], cervical cancer [35], breast cancer [36], and Hodgkin lymphoma survivors [37].”

Regarding the issue on possible metastatic sequelae to the brain, we have to consider two situations. First, do metastatic brain tumors cause stroke? The type of stroke associated with brain metastases is hemorrhagic stroke based on prior reports [13-15]. However, hemorrhagic stroke is not the main endpoint in our study. To our best knowledge, there were limited reports demonstrating the association of brain metastases and ischemic stroke in the English literature [16].

Second, is it possible misclassification of diseases between stroke and brain metastasis? We have performed further analysis for this issue, which we also mentioned in the specific minor comment #2 below. We found that 16 ovarian cancer patients who had been newly diagnosed with brain metastasis (ICD-9-CM code 198.3) within 3 months after stroke event. Because National Health Insurance Database in Taiwan did not contain patients' clinical symptoms and the images of CT/MRI, the diagnoses of brain metastasis or stroke were mainly based on the ICD-9-CM, which could be regarded as a comprehensive conclusion made by the clinicians according to all the clinically available information. Theoretically, some of them might be misclassification of diseases between stroke and brain metastasis, and others might be concurrent stroke and brain metastatic lesions. Even if we censored the 16 cases, the results still show statistical significance (adjusted hazard ratio 1.40; \( P < 0.001 \)). We would like to add the additional analysis in the Results section, and provided additional tables.

References in the reply:
13. Kondziolka D, Bernstein M, Resch L, Tator CH, Fleming JF, Vanderlinden RG, Schutz H: 
Significance of hemorrhage into brain tumors: clinicopathological study. *J Neurosurg* 1987, 


15. Wakai S, Yamakawa K, Manaka S, Takakura K: Spontaneous intracranial hemorrhage caused by 

Risk of intracranial hemorrhage and cerebrovascular accidents in non-small cell lung cancer 

Please refer to page 11, line 209–212 and Additional tables 2 and 3:

“These risk factors remained significant if 16 patients, who had a new diagnosis with brain 
metastasis (ICD-9-CM code 198.3) within 3 months after stroke event, were censored for 
analysis, on account of avoiding a short-term misclassification during acute brain insults 
(Additional tables 2 and 3).”

Additional table 2 Incidence of ischemic stroke in patients with and without ovarian cancer 
(excluding those with brain metastasis within 3 months after stroke)

<table>
<thead>
<tr>
<th>Patients with ovarian cancer</th>
<th>Patients without ovarian cancer</th>
<th>Crude HR (95% CI)</th>
<th>P value</th>
<th>Adjusted HR* (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of ischemic stroke</td>
<td>Per 1,000 person-years</td>
<td>No. of ischemic stroke</td>
<td>Per 1,000 person-years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total  251 8.8 245 6.9</td>
<td>1.29 (1.08–1.54) 0.005</td>
<td>1.40 (1.17–1.67) &lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50  182 14.7 206 12.2</td>
<td>1.22 (1.00–1.49) 0.051</td>
<td>1.26 (1.03–1.54) 0.023</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50  69 4.3 39 2.1</td>
<td>2.08 (1.40–3.08) &lt;0.001</td>
<td>2.09 (1.41–3.10) &lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.

* Adjusted for age, sex, and comorbidities including diabetes mellitus, hypertension, chronic kidney disease, 
dyslipidemia, coronary artery disease, atrial fibrillation, and peripheral arterial occlusive disease.

Additional table 3 Analyses of risk factors for ischemic stroke in patients with ovarian cancer 
(excluding those with brain metastasis within 3 months after stroke)

<table>
<thead>
<tr>
<th>Predictive variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysisa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Age ≥50</td>
<td>3.35 (2.53–4.42)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.00 (2.30–3.90)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.29 (2.57–4.22)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1.69 (1.15–2.48)</td>
<td>0.008</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2.20 (1.69–2.85)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3.90 (1.45–10.47)</td>
<td>0.007</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.80 (0.11–5.66)</td>
<td>0.819</td>
</tr>
<tr>
<td>PAOD</td>
<td>3.27 (0.46–23.30)</td>
<td>0.236</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>0.77 (0.59–0.99)</td>
<td>0.042</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>1.55 (1.15–2.08)</td>
<td>0.004</td>
</tr>
<tr>
<td>Cisplatin-based</td>
<td>1.34 (1.03–1.72)</td>
<td>0.026</td>
</tr>
<tr>
<td>Carboplatin-based</td>
<td>1.62 (1.26–2.09)</td>
<td>0.000</td>
</tr>
<tr>
<td>Non-platinum-based</td>
<td>1.32 (0.72–2.41)</td>
<td>0.369</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval; PAOD, peripheral arterial occlusive disease.

*a*All factors with *P* < 0.1 in univariate analyses were included in the Cox multivariate analysis.

*b*Treatment was analyzed as a time-dependent covariate in the Cox regression model.

### Specific minor comment #1:

1. **Survival of cancer stroke patients: This does not only depend on stroke, but also on cancer.**

**REPLY:** Thank you for your opinion. We agreed with your comment that the survival of cancer stroke patients would depend on both stroke and cancer. We therefore stated in the Background section that cerebrovascular complications would further deteriorate the clinical condition of cancer survivors.

Please refer to page 6, lines 92–95:

“However, the occurrence of comorbidities, such as cerebrovascular complications, after the cancer event may further exacerbate the tragedy in cancer survivors. In addition, the median survival after stroke in cancer patients is 4.5 months, and treatment has no survival benefit [4].”

We performed this study to establish the association of ovarian cancer and stroke, and to define possible risk factors. We believe that the topic of this manuscript warrants more clinical and research attention, and expect this article to be considered for publication as a research article in *BMC Medicine*. 
Specific minor comment #2:

2. Ref.: 6,7. Interesting, but paper 7 raises the point, if also CNS malignancies as metastasis or leptomeningeal disease were observed. Could it theoretically be, that this were added as stroke?

REPLY: Thank you for your comment that the possibility of misclassification between brain metastasis and stroke. First, the type of stroke associated with brain metastases is hemorrhagic stroke based on prior reports [13-15]. However, hemorrhagic stroke is not the main endpoint in our study. To our best knowledge, there were limited reports demonstrating the association of brain metastases and ischemic stroke in the English literature [16]. Second, we have performed further analysis for this issue. We found that 16 ovarian cancer patients who had been newly diagnosed with brain metastasis (ICD-9-CM code 198.3) within 3 months after stroke event. Because National Health Insurance Database in Taiwan did not contain patients' clinical symptoms and the images of CT/MRI, the diagnoses of brain metastasis or stroke were mainly based on the ICD-9-CM, which could be regarded as a comprehensive conclusion made by the clinicians according to all the clinically available information. Theoretically, some of them might be misclassification of diseases between stroke and brain metastasis, and others might be concurrent stroke and brain metastatic lesions. Even if we censored the 16 cases, the results still show statistical significance (adjusted hazard ratio 1.40; \( P < 0.001 \)). We would like to add the additional analysis in the Results section, and provided additional tables.

References in the reply:


Please refer to page 11, line 209–212 and Additional tables 2 and 3:

“These risk factors remained significant if 16 patients, who had a new diagnosis with brain metastasis (ICD-9-CM code 198.3) within 3 months after stroke event, were censored for analysis, on account of avoiding a short-term misclassification during acute brain insults (Additional tables 2 and 3).”
Additional table 2 Incidence of ischemic stroke in patients with and without ovarian cancer (excluding those with brain metastasis within 3 months after stroke)

<table>
<thead>
<tr>
<th>Predictive variables</th>
<th>Patients with ovarian cancer</th>
<th>Patients without ovarian cancer</th>
<th>Crude HR (95% CI)</th>
<th>P value</th>
<th>Adjusted HR* (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of ischemic stroke</td>
<td>Per 1,000 person-years</td>
<td>No. of ischemic stroke</td>
<td>Per 1,000 person-years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>251</td>
<td>8.8</td>
<td>245</td>
<td>6.9</td>
<td>1.29 (1.08–1.54)</td>
<td>0.005</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td>182</td>
<td>14.7</td>
<td>206</td>
<td>12.2</td>
<td>1.22 (1.00–1.49)</td>
<td>0.051</td>
</tr>
<tr>
<td>&lt;50</td>
<td>69</td>
<td>4.3</td>
<td>39</td>
<td>2.1</td>
<td>2.08 (1.40–3.08)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.

* Adjusted for age, sex, and comorbidities including diabetes mellitus, hypertension, chronic kidney disease, dyslipidemia, coronary artery disease, atrial fibrillation, and peripheral arterial occlusive disease.

Additional table 3 Analyses of risk factors for ischemic stroke in patients with ovarian cancer (excluding those with brain metastasis within 3 months after stroke)

<table>
<thead>
<tr>
<th>Predictive variables</th>
<th>Univariate analysis (HR (95% CI))</th>
<th>P value</th>
<th>Multivariate analysis (HR (95% CI))</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥50</td>
<td>3.35 (2.53–4.42)</td>
<td>&lt;.0001</td>
<td>2.19 (1.61–2.98)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.00 (2.30–3.90)</td>
<td>&lt;.0001</td>
<td>1.81 (1.34–2.44)</td>
<td>0.000</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.29 (2.57–4.22)</td>
<td>&lt;.0001</td>
<td>1.90 (1.43–2.53)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1.69 (1.15–2.48)</td>
<td>0.008</td>
<td>1.07 (0.72–1.59)</td>
<td>0.745</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2.20 (1.69–2.85)</td>
<td>&lt;.0001</td>
<td>1.02 (0.76–1.37)</td>
<td>0.907</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3.90 (1.45–10.47)</td>
<td>0.007</td>
<td>1.95 (0.72–5.29)</td>
<td>0.188</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.80 (0.11–5.66)</td>
<td>0.819</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAOD</td>
<td>3.27 (0.46–23.30)</td>
<td>0.236</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval; PAOD, peripheral arterial occlusive disease.
**Specific minor comment #3:**

3. Discussion: The stroke risk is estimated: "Our data revealed a 1.49-fold increased risk of developing ischemic stroke among patients with ovarian cancer". In the introduction it is 1.38. What is right?

**REPLY:** In the Results section of abstract and full text, we showed two hazard ratios (HRs), 1.38 and 1.49. The former was crude HR calculated with the Cox proportional hazard models to test the association between ovarian cancer and ischemic stroke, and the latter was HR further adjusted for age and comorbidities. To avoid misunderstanding, we added a short sentence in the Methods section, and revised the sentence in the Discussion section.

Please refer to page 9, lines 155–158 & page 11, lines 215–217:

“Hazard ratio (HR) and 95% CI were calculated with the Cox proportional hazard models to test the association between ovarian cancer and ischemic stroke; the HR would be further adjusted for age and comorbidities.”

“Our data revealed an increased risk of developing ischemic stroke with an adjusted HR of 1.49 among patients with ovarian cancer.”

Please also refer to page 4, lines 65–68 & pages 10–11, lines 191–197:

“After a median follow-up of 2.68 and 3.85 years, respectively, the ischemic stroke incidence was 1.38-fold higher in the ovarian cancer cohort than in the comparison cohort (9.4 vs. 6.8/1000 person-years), with an age- and comorbidity-adjusted HR of 1.49 ($P < 0.001$).”

“Compared to the matched cohort, the crude HR for subsequent ischemic stroke after ovarian cancer was 1.38 (95% CI 1.16 to 1.64; $P < 0.001$). After adjusting for age and comorbidities, the HR was 1.49 (95% CI 1.25 to 1.78; $P < 0.001$).”

**Specific minor comment #4:**

4. "Thromboembolism might contribute to cancer-related stroke, due to its high incidence in cancer patients." This is a very general statement. It could be made, if the stroke types were available.

**REPLY:** Thank you for your kind correction. Since we have clearly pointed that the stroke events were ischemic type, we have deleted this generally stated sentence, originally in page 12, line 224-225.
For the ischemic stroke defined in our study, please refer to page 8, lines 138–140:
“In our study, identification was made on the basis of ischemic stroke coding (ICD-9-CM code 436, 433.X, 434.X, and 437.1X), accompanied by computed tomographic (CT) or magnetic resonance (MR) images.”

Specific minor comments #5 & #6:
5. "In addition, the presence of disseminated intravascular coagulation in patients with ovarian cancer may indicate a hypercoagulative status" - There is no indication in the results, that this might have been the case.
6. "One direct evidence for the hypercoagulative state is the frequently overexpressed tissue factor in ovarian cancer tissue, which could activate the extrinsic coagulation cascade and cause thrombolic events in ovarian cancer patients [14]." - was this measured in the cohort?

REPLY: Thank you for kindly pointing out the limitation of our study. It's true that one of the limitations of the National Health Insurance Database in Taiwan is lack of biochemistry profile (e.g., coagulation profile such as prothrombin time, activated partial thromboplastin time, D-dimer, fibrinogen, and fibrin degradation product, etc), which was required for further exploration of coagulation disorder in these patients. Thus, we did not make any conclusion about the correlation between ovarian cancer and coagulation disorders. As we replied in the general comments #2, the limitation regarding biochemistry profile was added in the Discussion section.

And we need to state that the paragraph in the Discussion section (page 12, lines 230–239) may not serve the reflection of our laboratory results but the supporting evidences for our main finding: ovarian cancer patients were at an increased risk of developing ischemic stroke. We would like to indicate that our study concept was based on a widely-observed clinical condition, and the study design was on the basis of a theoretical hypothesis but not a random chance with statistical significance.

Please refer to page 14, lines 277–280:
“This study has several limitations. First, lifestyle variables and behavioral factors, such as tobacco and alcohol use, body mass index, dietary habits and biochemistry profile such as serum D-dimer level and disseminated intravascular coagulation profiles, were not available in the claims data of the Taiwan NHI.”

Specific minor comment #7:
7. Line 220-228: are in the same line and must be clearly stated as suggestions, and possible explanations. This study does not explain these phenomena.

REPLY: Thank you for the important suggestions. We realize that the result of our study does not
support these laboratory findings in selected ovarian cancer patients. On the contrary, the findings of laboratory studies serve as part of explanations for the result of our study. We had revised the sentences in the Discussion section.

Please refer to page 12, lines 234–239:
“Together, these findings suggest that a subgroup of ovarian cancer patients may have distinct coagulopathies making these patients vulnerable for specific vascular events, including ischemic stroke. They are also the possible explanations that ovarian cancer survivors in our study, especially among younger patients who had no established conventional stroke risk factors, possess a higher risk of subsequent ischemic stroke.”

Specific minor comment #8:
8. "Our study showed that ovarian cancer patients receiving chemotherapy, particularly platinum-based regimens, might have an additionally increased stroke risk. This effect was insignificant in non-platinum–based regimens. In prior studies, chemotherapy associated increased stroke was observed in patients with head-and-neck cancer." Comments on chemotherapy- see above.

REPLY: We appreciate your feedback. The association between ovarian cancer and subsequent ischemic stroke event is an important finding, even more interesting is that chemotherapy, especially platinum-based regimens, poses a significant risk to the stroke event. We have done a detailed literature review, and found many previous reports that may serve as part of explanations. As we replied in the general comments #3, we consider the results as our main findings, and discuss it thoroughly in the Discussion section.

Specific minor comment #9:
9. "diabetes mellitus, and chemotherapy treatment, following a diagnosis of ovarian cancer" possibly platinum drugs should be added here. "Chemotherapy" alone is too unspecific.

REPLY: Thank you for your suggestion. We have added the statement in the Discussion section.

Please refer to page 15, lines 292–295:
“Significant risk factors included age ≥ 50 years, hypertension, diabetes mellitus, and chemotherapy treatment, especially platinum-based regimens, following a diagnosis of ovarian cancer.”

Response to reviewer 3:

General comments #1:
As two referees have indicated that a specialist statistical review of this paper would be
beneficial, especially regarding the unequal period of follow-up for the two cohorts in the study, this paper has been passed to me for attention.

The paper is well written and the results clearly presented and discussed. As regards the seven points to consider when assessing the work, the answer is clearly “yes” to five of them:

1. Is the question posed by the authors new and well defined?
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
5. Are the discussion and conclusions well balanced and adequately supported by the data?
6. Do the title and abstract accurately convey what has been found?
7. Is the writing acceptable?

**REPLY:** We appreciate your positive feedback very much. We're glad to hear from you that our study design and statistical approach are approved by a statistical expert.

**General comments #2:**

As regards point 3 "Are the data sound and well controlled?", I note that the study is limited by the lack of information on risk factors such as smoking and alcohol consumption. This is recognized by the authors in the discussion in para. 8, but should not, of itself, preclude publication.

**REPLY:** We sincerely thank you for your careful reading and positive feedback. Your opinions are so important that it solves the puzzles of the other two reviewers regarding the unequal follow up period between the two groups. We are grateful to your affirmative on the data management and statistical methods we used.

**Specific discretionary comment #1:**

As regards point 2 "Are the methods appropriate and well described, and are sufficient details provided to replicate the work?", the only issue related to appropriateness. While it is clear that the statistical methods used by the authors (Cox regression, log rank test) do take into account the different lengths of the two groups, there are three points I would like to make, all of which might be regarded as discretionary revisions.

1. Table 2 and Results para. 4 make it clear that the increase in risk of stroke associated with ovarian cancer was higher in subjects aged <50 years than in those aged 50+ years old. However, there is no test of statistical significance of the two RRs. Based on the RRs and 95% CIs I estimate this as p = 0.015. If the authors agree, they might include p = 0.015, or p<0.05, after “was higher” in the text.

**REPLY:** Thank you for your kind suggestion. We have performed a test of statistical significance
and found out that the interaction crude \( P \) value and adjusted \( P \) value were 0.0098 and 0.0129 respectively. We have included the \( P < 0.05 \) after “was higher” in the Results section.

Please refer to page 10, lines 193–197:

“When the study subjects were stratified into two subgroups, the relative risk (RR) of stroke was higher (\( P < 0.05 \)) in subjects who were <50 years (adjusted HR 2.28; 95% CI 1.55 to 3.36; \( P < 0.001 \)) compared to those who were \( \geq 50 \) years old (adjusted HR 1.33; 95% CI 1.09 to 1.62; \( P = 0.005 \)) (Table 2).”

Specific discretionary comment #2:
2. Although the study design was based on ovarian cancer and individually matched controls, the methods of analysis do not take the matching into account. One simple way to do this would be to use McNemar’s test to compare (a) the number of case-control pairs where the case got a stroke while the control was still being followed up with (b) the number where the control got a stroke while the case was still being followed up.

**REPLY:** Thank you for the kind suggestion. The matching between the ovarian cancer and control cohort was not exactly matched in this study; each control individual could be fully matched according to age, but partially according to comorbidities, by means of “frequency matching” [17]. We thus used a simple chi-square test to show that the matching result is optimal for the subsequent analysis. If a McNemar’s test is preferred for publication, we would like to revise our manuscript.

References in the reply:

Specific discretionary comment #3:
3. Table 3 shows the results of a multivariate analysis of risk factors for ischaemic stroke in patients with ovarian cancer. It would be of some interest to see corresponding results for the controls, possible as an additional file, with brief reference to it in the text.

**REPLY:** Thank you for the important opinion. We performed an analysis on the effect of the risk factors in the control group and found out that age \( \geq 50 \), diabetes mellitus, and hypertension were all significant risk factors for stroke events with hazard ratios (HRs) of 3.89, 1.53, and 2.43 respectively. We believe that the matched control cohort is appropriate and representative.

Please refer to page 11, lines 203–204:

“Similarly, age \( \geq 50 \) years, diabetes mellitus, and hypertension were also independent risk factors for ischemic stroke in the control cohort (Additional table 1).”
Please also refer to Additional table 1 as below:

### Additional table 1 Analyses of risk factors for ischemic stroke in patients without ovarian cancer

<table>
<thead>
<tr>
<th>Predictive variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Age ≥50</td>
<td>5.99 (4.25–8.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.76 (2.11–3.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.39 (3.40–5.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1.55 (1.04–2.29)</td>
<td>0.030</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2.11 (1.62–2.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2.87 (1.07–7.71)</td>
<td>0.037</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4.74 (2.11–10.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral arterial occlusive disease</td>
<td>2.54 (0.36–18.13)</td>
<td>0.352</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.

*All factors with P < 0.1 in univariate analyses were included in the Cox multivariate analysis.