Addendum

J. Kang conceived the project, interpreted the data, and wrote the manuscript. H. Li wrote the manuscript. W. Chen conceived the project, wrote the manuscript, and gave final approval.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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Peripherally inserted central catheter-related deep vein thrombosis: contemporary patterns and predictors: reply

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We thank Drs Kang, Li and Chen for their thoughtful reply to our recently published manuscript 'Peripherally Inserted Central Catheter-Related Deep Vein Thrombosis:

Contemporary Patterns and Predictors' [1]. Drs Kang, Li and Chen note that our findings related to the association between PICC gauge, cancer and deep vein thrombosis (DVT) are in accord with the prior literature [2]. They, however, raise several interesting questions related to these and other findings in our paper. We address their concerns individually below.

First, Kang and colleagues suggest that cancer type and burden may influence the risk of DVT. We agree that this is often the case. In our study, 35% of the 301 patients with malignancies had advanced or metastatic disease at the time they were diagnosed with thrombosis. Considering this population separately using both logistic and Cox proportional hazards regression models, we did not find statistically significant differences in the risk of PICC-related thrombosis in patients with advanced cancer compared to patients without metastases (odds ratio [OR] = 2.06, 95% confidence interval [CI] = 0.94–4.43 vs. OR = 1.81, 95%CI = 0.74–4.45) (Table 1). While this finding may be limited by statistical power, another plausible explanation is the fact that tumor biology or disease extent are but one of many characteristics that influence the risk of thrombosis in patients with cancer [3]. For example, historical elements such as prior venous thromboembolism (VTE) and clinical aspects such as reduced mobility are also important in determining the risk of thrombosis in patients with and without cancer [4]. Furthermore, factors such as concurrent infections (commonly associated with immune-suppressive therapies) have been noted to increase the risk of thrombosis in patients with malignancy and PICCs specifically [5,6]. For these reasons, we have focused our analytical approach in PICC DVT on the presence of cancer and related risk factors, rather than type or stage of malignancy itself.

Second, the authors question whether the use of ICD-9 coding is a reliable method with which to measure VTE events given the potential overlap between other thrombotic events in this schema. As we worked with data from a national Veterans Affairs database, we were able to adequately parse superficial thromboses, upper and lower-extremity DVT from one another using a combination of both ICD-9 and procedure-specific codes within this data set. This approach increases the reliability of our findings and averts the typical limitations associated with ICD-9 data.

Third, the association between the presence of PICC, upper-extremity DVT and lower-extremity DVT is interesting and worthy of further discussion. As mentioned in our manuscript, we are in the process of analyzing data (now from over 72 000 patients) within which we continue to observe a strong, independent association between PICC placement and both upper and lower-extremity DVT. Early analysis of over 50 000 patients has been published in abstract form and shows that this relationship persists even after adjustment for a number of important confounders, including patient-, provider- and device-related characteristics [7]. Notably, this analysis is also not limited by ICD-9 codes as these data come from a multi-hospital consortium with direct abstraction of patient-level information. Therefore, while we concur that the epidemiology of upper-extremity DVT and that of lower-extremity DVT have historically been considered separate entities, we wonder whether this is the right paradigm when it comes to PICCs? For example, we hypothesize that PICC-DVT begins as a local process triggered by the presence of a catheter within a vein that often progresses to systemic activation of coagulation with distal manifestations. Further, because many patients who receive PICCs also harbor underlying risk factors for lower-extremity DVT (e.g. cancer and immobilization), it is not inconceivable that PICC placement serves as a trigger for both local and distal thromboses, including embolization of clots to the lung and development of lower extremity DVT. In this sense, the development of lower extremity thrombosis in patients with PICCs may simply 'unmask' those with an inherent propensity to develop thrombosis. Supportively, our analyses of over 72 000 patients suggests that symptomatic PICC DVT remains

Table 1 Predictors of PICC-thrombosis with additional covariates

	Logistic regression				Cox proportional hazards			
Variable	Odds ratio	Confidence interval		*P*-value	Hazard ratio	Confidence interval		*P*-value
Cancer								
Advanced/metastatic	2.055	0.980	4.306	0.06	2.030	0.971	4.245	0.06
Non-metastatic	1.758	0.732	4.222	0.21	1.701	0.718	4.028	0.23
None	1.000	Ref		Ref	1.000	Ref		Ref
Prior surgery (>1 h)	0.873	0.412	1.848	0.72	0.955	0.461	1.976	0.90
Prior VTE	1.400	0.307	6.334	0.67	0.992	0.207	4.761	0.99
French (gauge)								
4	1.000	Ref		Ref	1.000	Ref		Ref
5	1.867	0.858	4.062	0.12	2.182	1.005	4.735	0.05
6	2.348	0.823	6.698	0.11	3.318	1.187	9.275	0.02
COPD	1.378	0.691	2.746	0.36	1.498	0.747	3.002	0.26
Diabetes	0.962	0.495	1.872	0.91	0.962	0.497	1.861	0.91

Table 2 Characteristics of a valid conceptual framework*

Salient	A good model should selectively represent those variables that are most relevant to the outcome of interest
Accurate	The model should reflect an unbiased view of candidate predictors or domains based on the available evidence
Complete, yet parsimonious	The model should be as simple as possible, but no simpler. Variables of interest should be representative and valid
Perceptible	The model must be displayed in high-fidelity so that end-users may be able to easily apply it to problem-solving or clinical care
Understandable	The model should not be overly complicated or difficult to understand so as to limit its applicability
Predictive	The model should provide delineated key factors that are most associated with outcomes of interest
Falsifiable	The model should be testable such that domains and/or variables can be added or removed based on evolving data
Flexible	The model should be open to revision or changes based on accumulating evidence or data
Useful	Usefulness of a model is the sum of the above properties and reflects the extent to which a model can produce effective understanding and change

*Adapted from references 8 and 9.

associated with lower-extremity DVT following adjustment for a number of risk factors. We anticipate submitting this work for peer-review soon and look forward to continued discussion as to whether these disease states should be considered separate or a spectrum of severity in the specific case of PICCs.

Fourth, with respect to the interaction between PICC lumens and device diameter, we agree that these values are often correlated. However, most physicians do not consider PICC diameter when requesting a PICC; rather, many remain clinically attuned to number of lumens. While we acknowledge that the growing availability of smaller diameter multi-lumen PICCs is helpful, such devices are far from ubiquitous. Thus, use of alternate devices or clinical decision-aids that ensure the right device is ordered are highly appropriate and necessary steps. Notably, the assumption that a smaller PICC diameter will translate into lower VTE rates ignores the significance of other important characteristics (such as PICC tip location, dwell time and care processes). Thus, a composite approach that incorporates several patient-, provider- and device-related characteristics is needed to prevent this adverse outcome.

Fifth, we recognize the potential for confounding related to gender bias and mention these limitations within our manuscript. With respect to the incremental risk burden associated with diabetes and/or COPD, we are unsure if these clinical markers are more likely to cause thromboses in patients with cancer. While we are aware of the existence of studies that have suggested this association in non-cancer populations, repeat analyses with these variables revealed no differences in the observed estimates in both our logistic and Cox proportional hazards models (Table 1). Future studies that examine the incremental risk of these clinical factors are necessary to understand whether they are clinically meaningful in the context of the underlying hypercoaguable drive associated with malignancy and/or the presence of PICCs.

Finally, Drs Kang and colleagues state that our conceptual model may not be suitable for cancer or those with asymptomatic thrombosis. We respond by quoting the famous statistician, George E.P. Box, who once said, 'essentially all models are wrong, but some are useful'. In this spirit, we created a conceptual model that began first by looking within the evidence base. Our aim was to create a useful framework, one that researchers, clinicians and policy-makers alike could apply to any PICC-complication, not just DVT. Thus, like any good conceptual schema, our model had to meet several important characteristics (Table 2) [8,9]. Through our work to date, we believe our model for PICC-DVT meets many of these standards and are gratified that is has been applied successfully by others and us in the field [10,11]. However, future studies that adapt this conceptual framework to specific settings (e.g. asymptomatic thrombosis) or more specific patient cohorts (e.g. patients with cancer) would be welcomed. We encourage Dr Kang and colleagues to consider adapting and testing our framework for this purpose.

Disclosure of Conflict of Interest

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