LA3CK Score for Predicting in-Hospital Mortality after Minor Bleeding in Patients with Atrial Fibrillation

Ying Bai (✉ byfeixue@sina.com)

Beijing Tongren Hospital <https://orcid.org/0000-0002-7883-0368>

Xin-Yao Liu

Beijing Tongren Hospital

Yi-Xi Zou

Beijing Tongren Hospital

Shi-Dong Guo

Beijing Tongren Hospital

Zhen-Zhou Wang

Beijing Tongren Hospital

Xu-Bo Shi

Beijing Tongren Hospital

Peng Zhong

Beijing Tongren Hospital

Jing Chang

Beijing Tongren Hospital

Yu-Feng Sun

Beijing Tongren Hospital

Research article

Keywords: Atrial Fibrillation, Mortality, Minor Bleeding, LA3CK score

Posted Date: February 16th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-236768/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Backgrounds and Purposes Minor bleeding was found to be closely related with death in in-hospital patients with atrial fibrillation (AF) and the factors affecting mortality after minor bleedings were then explored.

Methods This study was divided into two parts. First, 15219 AF patients without major bleeding were included at their first hospitalizations from our centers since 2008 to 2018 to explore the association of minor bleeding with in-hospital mortality. Then factors related with in-hospital death were further explored in 789 AF patients with minor bleeding but without major bleeding and joined into one score predicting mortality after the minor bleedings during hospital stay.

Results Patients with minor bleedings were at high risk of mortality (Adjusted OR:4.61, 95% CI: 3.77-5.65, $p<0.001$), especially if they were older (Adjusted OR:1.05, 95% CI: 1.03-1.06, $p<0.001$), or complicated with chronic lung diseases, chronic kidney disease stage III-V, anemia, malignant tumor, acute myocardial infarction. The c-index was 0.681 using ROC curve when these risk factors were joined into the score LA3CK. The c-index was 0.81 when this score was extended to the whole in-hospital AF population.

Conclusions In the in-hospital AF patients, risk of mortality increased in patients with minor bleeding. The score LA3CK score had a good efficiency in predicting in-hospital mortality after minor bleedings.

Introduction

Atrial fibrillation (AF) is a common clinical arrhythmia with ageing.¹ Bleedings often accompany with AF, which are caused not only by adverse effects of antithrombotic drugs used for preventing stroke,² but also the complications easily leading to risk of bleeding, such as lung diseases, active malignancy, etc. Non-major bleeding and minor bleeding were shown to be associated with subsequent clinical events, such as risk of death, ischemic stroke and myocardial infarction.³⁻⁵ However, factors affecting mortality after minor bleedings were unclear. The physicians were still confused which kind of patients had higher risk of mortality after minor bleeding. We sought to explore the factors that have impact on the in-hospital mortality after minor bleedings in AF patients using data from clinical practice after confirming the relationship of minor bleeding and mortality during hospital stay. Then these factors were joined into one score predicting mortality after the minor bleedings in the in-hospital AF patients.

Methods

Study Patients

Selection process of the data was as previously described.⁶ Briefly speaking, 15688 AF patients with diagnosis of ICD 48 according to ICD 10th coding (I48xx01, I48xx02, I48xx03, I48xx04, I48xx05, I48xx06, I48xx07, I48xx08, I48xx09, I48xx10, I48xx11, I48xx12, I48xx13, I48xx14) were included at their first

hospitalizations from three hospitals (Beijing Tongren Hospital ranging from September 2008 to December 2018, Beijing Friendship Hospital ranging from January 2013 to March 2018, Capital Medical University and China-Japan Friendship Hospital ranging from April 2011 to May 2018). Details on patient demographics (e.g., age, sex), comorbidities, discharge status and in-hospital mortality could be obtained from the case reports.

This study was divided into two parts. First, after excluding 469 patients with major bleeding, 15219 AF patients were divided into two groups, minor bleeding group (N = 789) and no minor bleeding group (N = 14430). The association of minor bleeding with in-hospital mortality was explored in the whole population. Then further exploration of factors related with in-hospital mortality was performed in 789 AF patients with minor bleeding but without major bleeding.

Definitions of Bleeding

The corresponding copy of the inpatient records were obtained to confirm the diagnoses of any bleeding events, which were composite of major bleeding and minor bleeding. Major bleeding was defined as described in previous studies.^{7, 8} (1). Reduction in haemoglobin level of ≥ 2 g/L within 24 hours; (2). Transfusion of ≥ 2 units (U) of blood during the whole hospital stay; (3). Symptomatic bleeding in a critical area or organ; (4). Life-threatening bleeding (fatal bleeding, bleeding with a total decrease in haemoglobin level of ≥ 5 g/L, bleeding requiring inotropic agents or necessitating surgery). Bleeding that did not satisfy the definition of major bleeding was considered as minor bleeding.

Statistical Analysis

Data were expressed using mean $\pm$ SD for continuous variables and number (percentage %) for categorical variables. Continuous and categorical variables were compared using Chi-square test and unpaired Student's T test, respectively. Number of deaths in patients with minor bleeding was calculated. Logistic regression analyses using stepwise method were used to explore the association of minor bleeding with risk of mortality. Thereafter, factors affecting mortality after minor bleeding were explored using univariate and multivariate logistic regression in the minor bleeding group. Factors used in the multivariate analysis included sex, age, hypertension (HTN), diabetes mellitus (DM), dyslipidemia, heart failure (HF) history, acute myocardial infarction (AMI), anemia, chronic lung diseases (CLD), chronic kidney disease (CKD) stage III-V, which was defined according to The National Kidney Foundation/Kidney Disease Outcome Quality Initiative (NKF/K-DOQI), stroke/transient ischemic attack (TIA), malignant tumor (including active malignancy and malignant history). At last, factors with significant impact on the mortality after minor bleeding were joined into one score and the c-index was explored using ROC curve. $P < 0.05$ was considered as statistical significance. All statistical analyses were performed using SPSS 23.0 software (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

Baseline characteristics of the AF patients were shown in **Table 1**. Of these patients, 789 patients experienced minor bleeding and their distribution location sites were listed in Fig. 1. Patients who had minor bleeding were more likely to be older and had stroke/TIA history, dyslipidemia, DM history, HF history, AMI, CKD stage III-V, major bleeding history, CLD history, malignancy and anemia compared to those without minor bleeding. Of the patients with minor bleeding, the comparison of those died and survived was listed in **Table 1**, as well.

Table 1. Baseline characteristics of those died or survived due to minor bleeding

	The whole study population			After Minor Bleeding		
	No minor bleeding	Minor bleeding	p value	Survived	Died	p value
Number	14430	789	NA	576	213	NA
Age(y)	72.27 ± 11.65	77.19 ± 10.72	< 0.001	75.89 ± 10.71	80.70 ± 9.97	< 0.001
Female, N (%)	6429(44.6)	329(41.7)	0.12	244(42.4)	85(39.9)	0.57
Dyslipidemia	5486(38.0)	229(29.0)	< 0.001	180(31.3)	49(23.0)	0.03
Prior stroke/TIA	2072(14.4)	161(20.4)	< 0.001	122(21.2)	39(18.3)	0.43
HTN history	9708(67.3)	510(64.6)	0.13	379(65.8)	131(61.5)	0.28
DM history	4528(31.4)	215(27.2)	0.02	152(26.4)	90(29.6)	0.37
HF history	4869(33.7)	307(38.9)	0.003	208(36.1)	99(46.5)	0.009
AMI	1003(7.0)	147(18.6)	< 0.001	98(17.0)	49(23.0)	0.06
CKD stage III-V	2084(14.4)	226(28.6)	< 0.001	140(24.3)	86(40.4)	< 0.001
Major bleeding history	113 (0.8)	16(2.0)	0.001	13(2.3)	3(1.4)	0.58
Prior gastric disease	551(3.8)	111(14.1)	< 0.001	95(16.5)	16(7.5)	0.001
CLD	2823(19.6)	179(22.7)	0.03	112(19.4)	67(31.5)	< 0.001
Anemia	1598 (11.1)	319(40.4)	< 0.001	211(36.6)	108(50.7)	< 0.001
All Malignancy	2174(15.1)	163(20.7)	< 0.001	109(18.9)	54(25.4)	0.06
Antithrombotic therapy	2221(24.6)	78(16.5)	< 0.001	63(19.4)	15(10.1)	0.01
HTN, hypertension; DM, diabetes mellitus; HF, heart failure; AMI, acute myocardial infarction; CLD, chronic lung diseases; CKD, chronic kidney disease III-V, which was defined according to The National Kidney Foundation/Kidney Disease Outcome Quality Initiative (NKF/K-DOQI); TIA, transient ischemic attack; NA, not available.						

Association of risk of mortality with minor Bleeding

Minor bleeding could increase risk of mortality independently according to the results shown by unadjusted and adjusted logistic regression (adjusted OR: 4.61, 95% CI: 3.77–5.65, All p < 0.001).

(Table 2).

Table 2
Minor bleeding increased risk of in-hospital mortality in AF patients

	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
In-hospital mortality	8.07(6.77–9.63)	< 0.001	4.61(3.77–5.65)	< 0.001

Table 3
Risk of death after minor bleeding in AF patients during hospital stay

Death after minor bleeding				
	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Age	1.05(1.03–1.07)	< 0.001	1.05(1.03–1.06)	< 0.001
Female	0.90(0.66–1.25)	0.54	0.90 (0.64–1.27)	0.55
Dyslipidemia	0.66(0.46–0.95)	0.02	0.58(0.38–0.87)	0.009
Stroke outcome	0.79(0.51–1.20)	0.27	0.94(0.59–1.50)	0.8
HTN history	0.83(0.60–1.15)	0.26	0.70(0.48–1.01)	0.06
DM history	1.17(0.83–1.66)	0.37	1.28(0.87–1.88)	0.22
HF history	0.90(0.66–1.25)	0.54	1.36(0.96–1.92)	0.09
AMI	1.46(0.99–2.14)	0.06	1.77(1.14–2.76)	0.01
CKD stage III-V	2.11(1.51–2.94)	< 0.001	1.67(1.15–2.42)	0.007
Major bleeding history	0.62(0.18–2.19)	0.46	0.80(0.21–2.96)	0.73
Prior gastric disease	0.41(0.24–0.72)	0.002	0.44(0.25–0.79)	0.006
CLD	1.90(1.33–2.71)	< 0.001	1.67(1.13–2.46)	0.01
Anemia	1.78(1.30–2.44)	< 0.001	1.48(1.05–2.10)	0.03
All Malignancy	1.46(1.00-2.11)	0.05	1.61(1.06–2.44)	0.03
Abbreviations were shown in Table 1.				

Factors increased risk of mortality after minor bleeding

Older patients were inclined to develop into death if they experienced minor bleeding (Adjusted OR: 1.05, 95% CI: 1.03–1.06, $p < 0.001$) with the cutoff of age 80 years old. (Sensitivity=57.75% and specificity=62.50%). Other factors related with increased risk of mortality after minor bleedings included CLD, AMI, anemia, malignant tumor and CKD stage III-V.

LA3CK score

These risk factors were joined into one simple LA3CK score (Table 4). L: Chronic lung disease (1 point); A3: Age $\geq$ 80 years old /Acute myocardial infarction/Anemia (1 point each); C: cancer (including both malignant tumor history and active malignant tumor) (1 point); K: chronic kidney dysfunction (1 point). Total score ranged from 0 to 6 scores. The c-index of LA3CK score was 0.681 (95% CI:0.641–0.721) using ROC curve. (Fig. 2A). Patients with score $\geq$ 2 increased the risk of mortality by 4-fold after minor bleeding compared to those with score < 2 according to logistic regression. When we extend this score in the whole in-hospital AF population, we found the c-index of 0.811. (Fig. 2B).

Table 4
The LA3CK score

Alphabetic	Factors	Score
L	Chronic Lung Disease	1
A3		
	Age > 80 years old	1
	Acute myocardial infarction	1
	Anemia	1
C	Cancer (Malignant tumor history and active malignant tumor)	1
K	Chronic Kidney Disease Stage III-V	1

Discussion

Risk of mortality increased after minor bleeding in the in-hospital AF patients. Factors increased risk of mortality after minor bleeding included CLD, old age $\geq$ 80 years old), AMI, anemia, malignant tumor and CKD stage III-V. The c-index was 0.681 (95% CI:0.641–0.721) using ROC curve when these risk factors were joined into the LA3CK score.

Most studies focused on the increased risk of clinical outcomes caused by major bleeding.^{3,9} Actually, the minor bleeding was 1.6 times common compared with major bleeding in the current population, though less common compared with other trials testing oral anticoagulation.⁴ Similar to the results from the randomized control trial data,⁴ the minor bleeding was independently associated with subsequent risk of death using the data from clinical practice in AF patients. This study was performed after excluding the patients with major bleeding no matter if the major bleeding occurred following minor bleeding, thus we believed the possibility of impact caused by major bleeding was minimized to the utmost.

An increased risk of mortality after minor bleeding was found with ageing. Therefore, we believed that more attention should be taken for those with higher age, even if they had minor bleeding. Besides, the bleeding risk related with complications should be taken more seriously, as most of the bleedings were

caused by the complicated diseases (ie. hemoptysis caused by bronchiectasis, ocular hemorrhage related with hypertension or DM, tumor related bleeding, etc).

The risk factors derived from this exploratory analysis were involved into the LA3CK score, showing a good efficiency in predicting death after minor bleeding. This score was mainly constituted of underlying complicated diseases. Therefore, the score could be promptly deduced by a careful clinical evaluation, as only anemia caused by hemoglobin decrease was derived from laboratory examinations, which was also very important and necessary for diagnosing minor bleeding. Though unstandardized anticoagulation therapy was confirmed increasing risk of mortality, this factor changed a lot with the treatment process, which made it difficult to be involved into a score. The little need for instrumental and laboratory evaluation to calculate the individual risk of death facilitates the physicians and patients for clinical decisions. Furthermore, it would be helpful for risk stratification for predicting risk of death after minor bleeding using this specifically derived calibration methods.

Limitations

There are several limitations to be mentioned for the current analysis. First, this is a retrospective analysis collecting information from three central hospitals in Beijing. It is prudential to extend the results from the present study to a more extensive community because the dataset represented the selective in-hospital population. Second, definitions of variables were retrospectively reviewed, but were considered strictly built as uniform diagnosis and treatment guidelines were used in clinical practice in the Beijing District. Third, minor bleeding preadmitting into the hospitals was usually neglected by the patients, therefore, only major bleeding history was available for these patients. However, minor bleeding was particularly described in the records, and the minor bleeding information in hospital was accurate and believable. Fourth, mild to moderate anemia was usually not recorded in the case reports, therefore, the anemia information for those with mild to moderate anemia was not fully collected due to the data collection method which was mainly dependent on the diagnosis from the case reports. Besides, it is hard to differentiate the reason of anemia for all the in-hospital patients, as some may be caused by in-hospital bleeding and some may have long anemic history. Fifth, it is necessary to point out that tuberculosis was not included in the CLD due to diversity of the disease and lung cancer was not included in the CLD to avoid duplication recording with the malignant tumor. Sixth, malignant tumor included both malignant tumor history and active malignant. Above all, information from the case reports was mostly comprehensive and accurate which increased the robustness of the study. Seventh, this study mainly captured events that occurred during hospitalization. Therefore, whether exploration or generalization of in-hospital data could be made needed further exploration.

Conclusion

In the in-hospital AF patients, risk of mortality increased in patients with minor bleeding. The LA3CK score had a good efficiency in predicting in-hospital mortality after minor bleedings.

Declarations

Ethical Approval and Consent to participate

The authors are 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by clinical research ethics committee of our centers (NO.: TRECKY2020-097) and individual consent for this retrospective analysis was waived.

Consent for publication

Yes

Availability of supporting data

If necessary we can provide supporting data.

Competing interests

The authors have no conflicts of interest to declare.

Funding

This study was supported by grants from National Science Foundation of China (81800291), Beijing Municipal Administration of Hospitals' Youth Programme (QML20180207).

Authors' contributions

Ying Bai takes responsibility for the content of the manuscript, including the data and analysis. Yu-Feng Sun, Shi-Dong Guo, Peng Zhong Zhen-Zhou Wang, Peng Zhong, Jing Chang had full access to all of the data registry, outpatient records. Xin-Yao Liu Yi-Xi Zou, Xu-Bo Shi contribute greatly to the study design and data interpretation.

Acknowledgements

None.

Authors' information

Ying Bai, PhD;^a Xin-Yao Liu, MD;^a Yi-Xi Zou, PhD;^b Shi-Dong Guo, MD;^c Zhen-Zhou Wang, MD;^d Xu-Bo Shi, PhD;^a Peng Zhong, MD;^e Jing Chang;^f Yu-Feng Sun, MD^g

^a Cardiovascular Center, Beijing Tongren Hospital, Capital Medical University, Beijing, 100730, China;

^b Department of Cardiac Surgery, Beijing Anzhen Hospital, Capital Medical University, Beijing, 100029, China;

^c Emergency department of China-Japan Friendship Hospital, No. 2 Yinghua Dongjie, Hepingli, Chaoyang District, Beijing, 100029, China;

^d Trauma Medicine Center, Peking University People's Hospital, 100044, China.

^e Department of Ultrasound, Beijing Friendship Hospital, Capital Medical University, Beijing, 100050, China;

^f Cloud Medical Products Marketing Center

^g Clinical Medical Laboratory Beijing Tongren Hospital, Capital Medical University, Beijing, 100730, China;

Corresponding Authors:

Yi-Xi Zou, Department of Cardiac Surgery, Beijing Anzhen Hospital, Capital Medical University, Beijing, 100029, China Tel: +86-10-58268481; Fax: +86-10-58268481. E-mail: xihun00@sina.com.

OR

Yun-Feng Sun, Clinical Medical Laboratory Beijing Tongren Hospital, Capital Medical University, No.1, Dong Jiao Min Xiang Street, Dongcheng District, Beijing, 100730, China;

Tel: +86-10-58268481; Fax: +86-10-58268481. E-mail: trsunyufeng@163.com

References

1. Bai Y, Wang YL, Shantsila A, Lip GYH. The Global Burden of Atrial Fibrillation and Stroke: A Systematic Review of the Clinical Epidemiology of Atrial Fibrillation in Asia. *Chest*. 2017;152(4):810–20.
2. Bai Y, Guo SD, Deng H, Shantsila A, Fauchier L, Ma CS, et al. Effectiveness and safety of oral anticoagulants in older patients with atrial fibrillation: a systematic review and meta-regression analysis. *Age Ageing*. 2018;47(1):9–17.
3. Hylek EM, Held C, Alexander JH, Lopes RD, De Caterina R, Wojdyla DM, et al. Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin: The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, Characteristics, and Clinical Outcomes. *J Am Coll Cardiol*. 2014;63(20):2141–7.
4. Bahit MC, Lopes RD, Wojdyla DM, Held C, Hanna M, Vinereanu D, et al. Non-major bleeding with apixaban versus warfarin in patients with atrial fibrillation. *Heart*. 2017;103(8):623–8.
5. Patel NJ, Pau D, Nalluri N, Bhatt P, Thakkar B, Kanotra R, et al. Temporal Trends, Predictors, and Outcomes of In-Hospital Gastrointestinal Bleeding Associated With Percutaneous Coronary Intervention. *Am J Cardiol*. 2016;118(8):1150–7.

6. Bai YYQ, Sun H, Guo SD, Wang ZZ, Zhong P, Wei XY, Sun L, Shi XB, Liu YT. Prevalence and sex- and age-related risk of pulmonary embolism in inhospital patients with atrial fibrillation: a multicenter retrospective study from China. *Ann Transl Med* 2020.
7. Schulman S, Angeras U, Bergqvist D, Eriksson B, Lassen MR, Fisher W, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost*. 2010;8(1):202–4.
8. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981–92.
9. Held C, Hylek EM, Alexander JH, Hanna M, Lopes RD, Wojdyla DM, et al. Clinical outcomes and management associated with major bleeding in patients with atrial fibrillation treated with apixaban or warfarin: insights from the ARISTOTLE trial. *Eur Heart J*. 2015;36(20):1264–72.

Figures

Figure 1

The distribution of minor bleeding location sites

(A)

(B)

Figure 2

(A). ROC curve of the score in patients with minor bleeding predicting risk of death (c index = 0.681); (B). ROC curve of the score in the whole in-hospital patients predicting risk of death (c index = 0.811).