Thrombosis Research 176 (2019) 8–10

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Letter to the Editors-in-Chief

Regarding the necessity of an updated meta-analysis on the prognostic value of serum biomarkers in patients with pulmonary embolism

Pulmonary embolism (PE) is a common, potentially lethal condition and is the third leading cause of cardiovascular death [1]. Acute PE presents with a wide range of clinical manifestations from asymptomatic to death [2]. At the time of presentation, the mortality attributable to PE ranges from 9% in hemodynamically unstable patients to 3% in stable patients [3]. Current practice guidelines recommend thrombolytics in patients who are hypotensive at the time of presentation due to the high risk for short-term mortality [4]. Several studies have examined the role of right heart strain on echocardiography, biomarkers indicative of myocardial injury, and prognostic models to identify patients who are hemodynamically stable but at intermediate-high risk of poor outcomes [5]. Many biomarkers such as troponin, brain natriuretic peptides (BNP) or N-terminal pro BNP, heart-type fatty acid-binding protein (H-FABP) and D-dimer have been evaluated to identify subgroups of patients with poor prognosis. However, the ideal choice of biomarker, and the ideal cut-point remain controversial. Many systematic reviews and meta-analyses have summarized the evidence on the prognostic value of these biomarkers in patients with acute normotensive PE.

The US National Cancer Institute and the European Organization for Research and Treatment of Cancer suggested the development of comprehensive reporting guidelines to help those investigating the prognostic utility of tumour biomarkers in order to conduct studies in a more transparent manner. Ultimately, the recommendations aimed to enable a better evaluation of the utility of prognostic data. Consequently, McShane et al. (2005) published the Reporting recommendations for tumour marker prognostic studies (REMARK) checklist, which comprises of 20 items [6]. Using this checklist as a guide, we proposed six key features that are critical to employ in a study's design in the context of prognosticating patients with PE using biomarkers: the studies should be prospective; included patients should be consecutive; patients should be from an unselected VTE population; clinical endpoints of all-cause mortality, death from VTE or composite of adverse events should be clearly defined; the timing of the end points should be predefined; the type of biomarker assay utilized should be stated and the lab cut-off value for an abnormal value should be determined a priori. The purpose of this study was to evaluate the inclusion criteria of published meta-analyses summarizing the use of serum biomarkers to prognosticate outcomes in PE against these key features of the REMARK checklist to assess the quality of their prognostic data.

1. Methods

To assess the degree to which published meta-analyses evaluating the prognostic value of biomarkers used these key features in their inclusion criteria, we conducted a systematic search through Medline, Ovid and the Cochrane Central Register of Controlled Trials from inception through June 2, 2017. We surveyed the literature for studies on the prognostic utility of D-dimer, BNP, N-terminal pro BNP, FABP, and troponins in patients with pulmonary embolism. The inclusion criteria for this analysis were: (1) study must be a meta-analysis in design, (2) must prognosticate any clinical outcome related to PE using any of the aforementioned biomarkers. We identified 13 meta-analyses published between 2007 and 2016 that met our inclusion criteria. Since quality is usually determined using the "(A) Measurement Tool to Assess Systematic Reviews" (AMSTAR) tool we evaluated the AMSTAR score to illustrate that the quality of the methods of the meta-analysis but does not necessarily mean the reported data is useful [7]. If the six criteria we drew from the REMARK criteria are not elements of the studies included in the meta-analysis we argue the results are less useful, perhaps not useful. The meta-analyses were also evaluated on their reporting of the quality of the studies they included. Furthermore, the degree to which the meta-analyses' assessment of quality considered the features described by the "Quality in Prognosis Studies" (QUIPS) Tool was evaluated [8]. The QUIPS Tool allows researchers to grade the validity and bias of prognostic studies based upon six domains: study participation, study attrition, prognostic factor measurement, confounding measurement and account, outcome measurement, and analysis and reporting [8].

2. Results and discussion

Table 1 outlines the 13 meta-analyses identified by biomarker assessed and their final AMSTAR evaluation. Eleven were of medium quality and 2 were high quality. However, an assessment of the study selection criteria of the papers eligible for inclusion in each meta-analysis revealed that none of them considered all six of the proposed criteria we generated from the REMARK tool. Namely, two of the studies considered 2/6 of the proposed criteria, three studies considered 3/6, six studies considered 4/6 and two studies considered 5/6 criteria. Notably, none of the studies required that the lab cutoff value to indicate an abnormally elevated biomarker be determined a priori. This allowed the inclusion of studies that retrospectively determined an optimal biomarker cutoff value into these meta-analyses. Six meta-analyses included retrospective studies, 10 did not mandate consecutive unselected PE patients, and two did not necessitate the type of biomarker assay utilized to be stated as one of their inclusion criteria. As such we question the utility of the conclusions and suggest an updated meta-analysis that is more rigorous and includes only studies that utilized proper methods for the evaluation of prognostic markers, be performed.

https://doi.org/10.1016/j.thromres.2019.02.005
Received 11 December 2018; Received in revised form 28 January 2019; Accepted 4 February 2019
Available online 05 February 2019
0049-3848/ © 2019 Elsevier Ltd. All rights reserved.

Table 1
Assessment of the inclusion criteria and quality of meta-analyses on prognostic biomarkers of PE.

First author (year)	Journal	Biomarkers	Main study results (all-cause mortality; OR and 95% CI)[a]	AMSTAR quality	Prospective study	Consecutive and unselected	Clinical endpoint defined	Timing of clinical endpoint stated	Laboratory assay stated	A priori lab cut-off value
Bajaj A (2015) [9]	Lung	Troponin, BNP, NT-proBNP, H-FABP	Troponin: OR = 4.80 (3.25–7.08) BNP or NT-proBNP: OR = 7.98 (4.34–14.67)	Medium	No	No	Yes	Yes	Yes	No
Bajaj A (2015) [2]	Heart & Lung	Troponin	OR = 4.80 (3.25–7.08)	Medium	No	No	Yes	Yes	Yes	No
Jiménez (2009) [12]	Chest	Troponin	OR = 4.26 (2.13–8.50)	High	Yes	No	Yes	Yes	Yes	No
Becattini C (2007) [13]	Circulation	Troponin	OR = 5.24 (3.28–8.38)	Medium	No	No	Yes	Yes	Yes	No
Coutance G (2008) [14]	Critical Care	BNP	OR = 6.57 (3.11–13.91)	Medium	Yes	No	Yes	Yes	Yes	No
Cavallazzi R (2008) [15]	Intensive Care Med	BNP, NT-proBNP	BNP: OR = 6.0 (1.31–27.43) NT-proBNP: OR = 16.12 (3.1–83.68)	Medium	No	No	Yes	Yes	No	No
Klok FA (2008) [16]	Am J Respir Crit Care Med	BNP, NT-proBNP	BNP or NT-pro-BNP: OR = 7.6 (3.4–17)	Medium	Yes	Yes	Yes	Yes	Yes	No
Lega JC (2009) [17]	Thorax	Troponin, BNP	BNP: OR = 6.2 (3.0 to 12.7)	High	Yes	Yes	Yes	Yes	Yes	No
Bajaj A (2015) [18]	J. Crit Care	H-FABP	PE-related Morality: OR = 32.94 (8.80–123.21)	Medium	Yes	No	Yes	Yes	Yes	No
Liu M (2015) [10]	Thrombosis Res.	H-FABP	NA	Medium	Yes	No	Yes	Yes	Yes	No
Ruan LB (2014) [19]	Chest	H-FABP	OR = 40.78 (11.87–140.09)	Medium	Yes	No	Yes	Yes	Yes	No
Becattini C (2012) [11]	J Thromb Thrombolysis	D-Dimer	OR = 2.76 (1.83–4.14)	Medium	No	No	Yes	Yes	No	No
Sanchez O (2008) [20]	Eur Heart J	BNP, NT-proBNP, troponin	BNP: OR = 9.5 (3.2–28.6) NT-proBNP: OR = 5.7 (2.2–15.1) Troponin: OR = 8.3 (3.6–19.3)	Medium	No	Yes	Yes	Yes	Yes	No

[a] OR = odds ratio; CI = confidence interval; NA = not applicable.

In the 13 meta-analyses we evaluated, five reported on the quality of their included studies. In these, the domains/check points as described in the QUIPS Tool were not fully met by the included studies. In the eight meta-analyses that did not report on study quality, our evaluation suggests (Table 1) that most did not determine if the included studies met our definition of good quality as per the REMARK checklist or the QUIPS Tool criteria.

In conclusion, the studies used in the meta-analyses published to date are not rigorous in terms of their design and methodological quality, and revealed inconclusive evidence on the utility of biomarkers to prognosticate patients with PE. Multiple prospective studies on normotensive patients with acute PE have been published. An updated meta-analysis that only includes studies that employ sound methods for the evaluation of prognosis is needed to clarify the prognostic role of biomarkers in clinical practice.

Conflict of interest

None of the authors have competing interests to disclose. Dr. Wells reports grant support fees from Bayer Healthcare, BMS and Pfizer, as well as personal fees from Bayer Healthcare, Itreas, Daiichi Sankyo and Janssen Scientific outside the submitted work.

References

[1] S.Z. Goldhaber, H. Bounameaux, Pulmonary embolism and deep vein thrombosis, Lancet 379 (2012) 1835–1846.
[2] A. Bajaj, M. Saleeb, P. Rathor, et al., Prognostic value of troponins in acute nonmassive pulmonary embolism: a meta-analysis, Heart Lung 44 (2015) 327–334.
[3] S. Laporte, P. Mismetti, H. Décousus, et al., Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry, Circulation 117 (2008) 1711–1716.
[4] S.Z. Goldhaber, L. Visani, M. De Rosa, Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER), Lancet 353 (1999) 1386–1389.
[5] D. Barrios, R. Morillo, R.D. Yusen, et al., Pulmonary embolism severity assessment and prognostication, Thromb. Res. 163 (2018) 246–251.
[6] L.M. McShane, D.G. Altman, W. Sauerbrei, et al., Reporting recommendations for tumor marker prognostic studies (REMARK), J. Natl. Cancer Inst. 97 (2005) 1180–1184.
[7] B.J. Shea, J.M. Grimshaw, G.A. Wells, et al., Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews, BMC Med. Res. Methodol. 7 (2007) 10.
[8] J.A. Hayden, D.A. van der Windt, J.L. Cartwright, et al., Assessing bias in studies of prognostic factors, Ann. Intern. Med. 158 (2013) 280–286.
[9] A. Bajaj, P. Rathor, V. Sehgal, et al., Prognostic value of biomarkers in acute nonmassive pulmonary embolism: a systematic review and meta-analysis, Lung 193 (2015) 639–651.
[10] M. Liu, X. Yuan, X. Qiu, et al., Prognostic role of heart-type fatty acid binding protein in pulmonary embolism: a meta-analysis, Thromb. Res. 135 (2015) 20–25.
[11] C. Becattini, A. Lignani, L. Masotti, et al., D-dimer for risk stratification in patients with acute pulmonary embolism, J. Thromb. Thrombolysis 33 (2012) 48–57.
[12] D. Jiménez, F. Uresandi, R. Otero, et al., Troponin-based risk stratification of patients with acute nonmassive pulmonary embolism: systematic review and metaanalysis, Chest 136 (2009) 974–982.
[13] C. Becattini, M.C. Vedovati, G. Agnelli, Prognostic value of troponins in acute pulmonary embolism: a meta-analysis, Circulation 116 (2007) 427–433.
[14] G. Coutance, O. Le page, T. Lo, et al., Prognostic value of brain natriuretic peptide in acute pulmonary embolism, Crit. Care 12 (2008) R109.
[15] R. Cavallazzi, A. Nair, T. Vasu, et al., Natriuretic peptides in acute pulmonary embolism: a systematic review, Intensive Care Med. 34 (2008) 2147–2156.
[16] F.A. Klok, I.C. Mos, M.V. Huisman, Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with pulmonary embolism: a systematic review and meta-analysis, Am. J. Respir. Crit. Care Med. 178 (2008) 425–430.
[17] J.C. Lega, Y. Lacasse, L. Lakhal, et al., Natriuretic peptides and troponins in pulmonary embolism: a meta-analysis, Thorax 64 (2009) 869–875.
[18] A. Bajaj, P. Rathor, V. Sehgal, et al., Risk stratification in acute pulmonary embolism with heart-type fatty acid-binding protein: a meta-analysis, J. Crit. Care 30 (2015) (1151.e1-7).
[19] L.B. Ruan, L. He, S. Zhao, et al., Prognostic value of plasma heart-type fatty acid-binding protein in patients with acute pulmonary embolism: a meta-analysis, Chest 146 (2014) 1462–1467.
[20] O. Sanchez, L. Trinquart, I. Colombet, et al., Prognostic value of right ventricular dysfunction in patients with haemodynamically stable pulmonary embolism: a systematic review, Eur. Heart J. 29 (2008) 1569–1577.

Harrish Nithianandan, Aoife Reilly, Philip Wells*
University of Ottawa, Ottawa Hospital Research Institute, The Ottawa Hospital, 501 Smyth Road, Ottawa, ON K1H 8L6, Canada
E-mail address: pwells@toh.ca (P. Wells).

* Corresponding author at: Department of Medicine, The Ottawa Hospital, General Campus, Suites M1840 - M1859, Box 206, 501 Smyth Road, Ottawa, ON K1H 8L6, Canada.