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Full Length Article

Diagnostic accuracy of four different D-dimer assays: A post-hoc analysis of the YEARS study



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ABSTRACT

Introduction: For exclusion of pulmonary embolism (PE) clinical decision rules in combination with a D-dimer assay are applied. Currently available D-dimer assays are not standardized and it is unknown whether these differences have an impact on diagnostic management of suspected PE. Therefore, the aim is to explore differences between D-dimer assays and their impact on diagnostic outcome.

Methods: Data from all patients included in the YEARS study were collected. The YEARS study is a prospective, multicentre, cohort outcome study evaluating 3462 patients with suspected PE in which four different D-dimer assays were applied (Liatest, Innovance, Tinaquant, Vidas). Median D-dimer concentrations were calculated for each D-dimer assay. Sensitivity, specificity, PPV and NPV for detection of PE of all four assays were determined in patients without YEARS items and in those with ≥ 1 YEARS items (i.e. symptomatic deep vein thrombosis, haemoptysis, and whether PE is the most likely diagnosis).

Results: A total of 1323, 1100, 768 and 271 D-dimer concentrations were collected using the Liatest Innovance, Tinaquant and Vidas assay, respectively. Median D-dimer concentrations differed significantly between assays, with lowest values in the Tinaquant assay. In patients without YEARS items using a cutoff level of 1000 ng/mL, the NPV varied from 99,5 to 100%. In patients with ≥ 1 YEARS items using a 500 ng/mL cutoff, the NPV varied from 97,0 to 100% depending on the assay.

Conclusions: The overall high NPV for all assays demonstrates the clinical value of the D-dimer assay. However, these results confirm differences between D-dimer assays, which have an impact on follow-up imaging. This emphasizes the need for standardization of D-dimer assays.

1. Introduction

An accurate D-dimer measurement is essential for a correct diagnosis and treatment of thrombosis based on red thrombi [1]. However, currently available D-dimer assays are not standardized. Several publications have reported a significant degree of variability in test results between different assays [2,3]. This is also evident when reviewing the

results of external quality control programs such as the program provided by the ECAT Foundation that includes approximately 650 participating laboratories worldwide (Fig. 1). It has however not been demonstrated whether standardization would benefit patients.

For exclusion of pulmonary embolism (PE) clinical decision rules in combination with a D-dimer measurement are applied. In the widely used Wells algorithm, the D-dimer concentration is only measured to

Abbreviations: CTPA, computer tomography pulmonary angiography; DVT, deep vein thrombosis; IQR, interquartile range; NA, not applicable; NPV, negative predictive value; PE, pulmonary embolism; PPV, positive predictive value; SD, standard deviation; WHO, World Health Organization.

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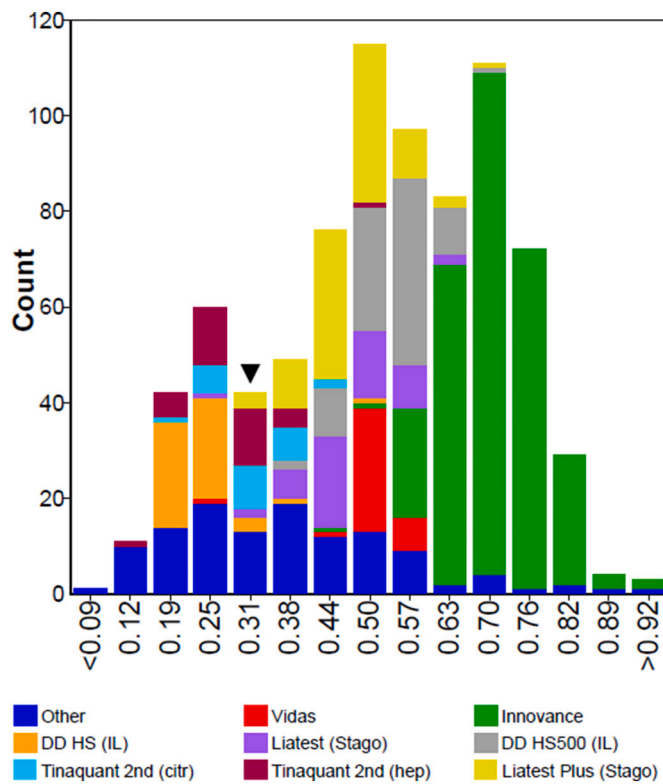


Fig. 1. Results from a sample from the ECAT External quality assessment program that was analyzed for D-dimer concentration with different assays in 645 different laboratories.

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rule out PE in patients with an unlikely or non-high pre-test probability of PE [4,5]. We recently showed that PE can be excluded safely by the YEARS diagnostic algorithm in patients with suspected PE [6]. This YEARS algorithm differs from the Wells algorithm, in the way that a pre-test probability dependent D-dimer threshold is applied.

Using the YEARS algorithm, patients with suspected PE are managed by simultaneous assessment of the YEARS clinical decision rule and measurement of D-dimer concentrations. The clinical decision rule consists of three YEARS items: 1) clinical signs of deep vein thrombosis (DVT), 2) haemoptysis, and 3) whether PE is the most likely diagnosis [6]. PE is considered excluded without a need for CT pulmonary angiography (CTPA) in patients without YEARS items and D-dimer concentrations less than 1000 ng/mL, or in patients with ≥ 1 YEARS items and D-dimer concentrations less than 500 ng/mL [6].

The safety of this algorithm was confirmed during 3 months follow-up in all patients in whom PE was excluded without CTPA in two management studies [6,7]. The main advantage of this algorithm was a 14% absolute reduction of CTPA examinations [6]. In the recent Artemis study in which the pregnancy-adapted YEARS diagnostic algorithm was assessed, a CTPA was avoided in 39% of pregnant women with suspected PE compared to the application of the conventional D-dimer threshold, saving costs, time and radiation exposure [7]. Furthermore, the simultaneous assessment of D-dimer and the clinical decision rule makes it an attractive and easy tool to apply during busy acute clinical practice.

Previous studies on the accuracy of the D-dimer assays mainly evaluated the exclusion of PE in patients with a non-high pre-test probability of PE with the predetermined cutoff level 500 ng/mL or an age adjusted cutoff level [4,8]. Since the YEARS algorithm the cutoff level 500 ng/mL is only applied in patients with ≥ 1 YEARS items and an additional higher D-dimer cutoff level is used in patients without YEARS items, it is relevant to investigate if the differences between the assay performances have an impact on the diagnostic accuracy of the D-dimer

test in this setting.

Therefore we performed a post-hoc analysis of the YEARS study in order to evaluate potential differences between D-dimer assays and their impact on diagnostic management and outcome.

2. Materials and methods

Data of all patients included in the YEARS study were used. For this prospective, multicentre, cohort outcome study 3465 patients were included between Oct 5, 2013 and July 9, 2015 [6]. The study was carried out in 12 hospitals in the Netherlands. Four different D-dimer assays were applied according to local practice each on the systems from the same manufacturers as the reagents: Vidas D-dimer (Biomerieux, Marcy-L'Étoile, France), Tinaquant (Roche Diagnostica, Mannheim, Germany), Liatest (Diagnostica Stago, Asnieres, France), and Innovance (Siemens, Marburg, Germany).

In the current analysis, patients were stratified according to the D-dimer assay that was applied at presentation according to local practice. Three patients from whom precise D-dimer levels were unavailable were excluded from the analysis.

Baseline characteristics and D-dimer concentrations of the patients in the different assay groups were described. Subsequent ANOVA analyses were performed to assess statistical differences between the four assays.

Median D-dimer concentrations were calculated per assay, stratified for the presence of PE. As gold standard patients were positive for PE when PE was diagnosed at baseline after CTPA imaging, or VTE was confirmed or could not be excluded as cause of death at 3 month follow up. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with the 95% confidence interval of all four assays were determined in patients without YEARS items and patients with ≥ 1 YEARS items [6].

3. Results

Four different D-dimer assays were applied, with each hospital using its own method for local clinical practice. Of the 3462 patients in the YEARS study D-dimer concentrations were analyzed with the Liatest, Innovance, Tinaquant and Vidas assay in 1323, 1100, 768 and 271 patients, respectively. Four out of 12 participating hospitals were academic medical centers. Table 1 summarizes the baseline characteristics. Baseline characteristics differed between the various D-dimer groups. For instance, compared to other D-dimer groups, there were lower rates of outpatients in the Innovance group, a lower rate of cancer and immobilization in the Tinaquant group, and a higher proportion of patients with ≥ 1 YEARS items in the Vidas assay group.

Table 2 summarizes the median D-dimer concentrations and the number of patients with a D-dimer concentration below the cutoff level (1000 or 500 ng/mL) in patients without YEARS items and patients with ≥ 1 YEARS items. The percentages of patients below the cutoff level correspond to the proportion of patients in whom PE was excluded without further CTPA analysis. This percentage varied from 71% to 82% in patients without YEARS items and from 15 to 29% in patients with ≥ 1 YEARS items among the different used D-dimer assays.

Table 3 summarizes the median D-dimer concentrations in patients diagnosed with and without PE with the four different assays. In patients without PE significant differences were found between assays and D-dimer concentrations varied from 320 to 790 ng/mL. In this group lowest D-dimer concentrations were found with the Tinaquant assay (320 ng/mL) and highest concentrations were found with the Vidas assay (790 ng/mL). Median D-dimer concentrations were approximately 5 times higher in patients with PE. No significant differences between D-dimer assays were found in patients with PE.

Sensitivity, specificity, PPV and NPV with the 95% confidence interval of all four D-dimer assays in patients without YEARS items as a diagnostic tool for pulmonary embolism are shown in Table 4. In patients without YEARS items in which a cutoff level of 1000 ng/mL was

Table 1
Baseline characteristics of patients with suspected pulmonary embolism divided per assay.

	All patients	Liatest	Innovance	Tinaquant	Vidas	P value
N	3462	1323	1100	768	271	N.A.
Mean age (years (SD))	53 (18)	54 (18)	52 (18)	53 (20)	59 (17)	<0,001
Women (%)	62,2%	61,7%	58,4%	68,0%	63,5%	<0,001
Median duration of complaints (days)	3	3	2	4	3	<0,001
Immobilization or surgery in the past 4 weeks	12,1%	14,9%	11,4%	7,3%	10,3%	<0,001
Outpatient	86,3%	94,3%	75,5%	83,7%	98,5%	<0,001
History of pulmonary embolism or deep vein thrombosis	10,4	11,6%	9,2%	9,4%	11,8%	0,365
Malignancy	9,6	12,5%	10,4%	3,6%	9,6%	<0,001
Patients with ≥ 1 YEARS item	50%	59%	40%	37%	80%	<0,001
Patients included in academic medical centers	51%	65%	81%	0	0	<0,001
Nr of hospitals that included patients	12	4	5	2	1	N.A.

Table 2
Median D-dimer concentrations and the number of patients (%) with a D-dimer concentration below the cutoff level in patients without YEARS items and patients with ≥ 1 YEARS items.

		Liatest	Innovance	Tinaquant	Vidas	P value
Patients without YEARS items	Number of patients	547	659	483	53	
	D-dimer (ng/mL) (median (IQR))	563 (756)	460 (700)	270 (450)	570 (690)	<0.001
	D-dimer <1000 ng/mL (n (%))	387 (71%)	499 (76%)	395 (82%)	39 (74%)	
Patients with ≥ 1 YEARS items	Number of patients	776	441	285	218	
	D-dimer (ng/mL) (median (IQR))	1009 (1931)	970 (1493)	770 (1580)	1100 (1805)	0.023
	D-dimer <500 ng/mL (%)	145 (19%)	70 (16%)	83 (29%)	33 (15%)	

Table 3
D-dimer concentrations in patients diagnosed with and without PE with the four different assays.

		Liatest	Innovance	Tinaquant	Vidas	P value
Patients without PE	Number of patients	1104	1000	676	223	
	D-dimer (ng/mL) (median (IQR))	666 (826)	565 (790)	320 (538)	790 (950)	<0.001
Patients with PE	Number of patients	219	210	92	48	
	D-dimer (ng/mL) (median (IQR))	3083 (3371)	2690 (3095)	2890 (5485)	3700 (3600)	0.709

Table 4
Sensitivity, specificity, PPV and NPV with the 95% confidence interval of all four assays (Liatest, Innovance, Tinaquant, Vidas) in patients without YEARS items using a D-dimer cutoff level of 1000 ng/mL.

	All assays	Liatest	Innovance	Tinaquant	Vidas
Sensitivity	93,8%	93,1%	92,9%	95,0%	100,0%
	(84,2–98,0)	(75,8–98,8)	(64,2–99,6)	(73,1–99,7)	(19,8–100,0)
Specificity	78,5%	74,3%	77,2%	85,1%	76,5%
	(76,4–80,4)	(70,3–78,0)	(73,7–80,4)	(81,4–88,1)	(62,2–86,8)
PPV	14,5%	16,9%	8,1%	21,6%	14,3%
	(11,3–18,2)	(11,6–23,8)	(4,6–13,8)	(13,8–31,9)	(2,5–43,8)
NPV	99,7%	99,5%	99,8%	99,7%	100,0%
	(99,1–99,9)	(97,9–99,9)	(98,7–100,0)	(98,4–100,0)	(88,8–100,0)

applied, the NPV varied from 99,5 to 100% depending on the assay (Table 4). In four patients without YEARS items a VTE related event was falsely excluded with a D-dimer value below 1000 ng/mL. Two of these four patients were in the Liatest group in whom D-dimer values of 898 and 609 ng/mL were found, while at the three month follow up a PE

could not be excluded as a cause of death. One of these four patients belonged to the Innovance group in whom a DVT was missed 14 days after surgery, while a D-dimer level of 560 ng/mL was measured. The last of these four patients was in the Tinaquant group in which a D-dimer level of 610 ng/mL was measured, while the patient was diagnosed with

Table 5
Sensitivity, specificity, PPV and NPV with the 95% confidence interval of all four assays (Liatest, Innovance, Tinaquant, Vidas) in patients with ≥ 1 YEARS items using a D-dimer cutoff level of 500 ng/mL.

	All assays	Liatest	Innovance	Tinaquant	Vidas
Sensitivity	99,3%	100,0%	100,0%	97,4%	97,9%
	(97,7–99,8)	(97,6–100,0)	(94,9–100,0)	(90,0–99,5)	(87,3–99,9)
Specificity	25,0%	25,0%	19,9%	38,8%	18,7%
	(22,7–27,5)	(21,6–28,8)	(16,0–24,6)	(32,2–45,7)	(13,3–25,5)
PPV	29,2%	31,1%	24,3%	36,6%	24,9%
	(26,9–31,7)	(27,5–34,9)	(20,0–29,0)	(30,3–43,7)	(18,9–31,8)
NPV	99,1%	100,0%	100,0%	97,6%	97,0%
	(97,2–99,8)	(96,8–100,0)	(93,5–100,0)	(90,8–99,6)	(82,5–99,8)

subsegmental PE on CTPA during admission.

Sensitivity, specificity, PPV and NPV with the 95% confidence interval of all four D-dimer assays in patients with ≥ 1 YEARS items as a diagnostic tool for pulmonary embolism are shown in Table 5. In patients with ≥ 1 YEARS items, in which a cutoff level of 500 ng/mL was applied, the overall NPV was 99,1%. When calculated separately for each assay, the NPV varied from 97,0 to 100% (Table 5). In three patients with ≥ 1 YEARS items a non-fatal PE was falsely excluded with a D-dimer value below 500 ng/mL. Two of these three patients were in the Tinaquant group with D-dimer levels of 380 and 410 ng/mL. One of these three patients was in the Vidas group, with a D-dimer concentration of 420 ng/mL. In these former three patients with a non-fatal PE with D-dimer values below the cutoff level, the CTPA was made at baseline and this was considered protocol violation.

4. Discussion

This post-hoc analyses of the YEARS study confirms the clinical value of the D-dimer assay since large differences in D-dimer values are shown in patients with and without PE. However, the present analyses show considerable differences in D-dimer concentrations between assays. Depending on the assay, the percentage of patients without YEARS items who had a D-dimer concentration below the cutoff level (1000 ng/mL) varied from 71% to 82%. In patients with ≥ 1 YEARS items, this percentage below the cutoff level (500 ng/mL) varied from 15% to 29% depending on the assay, resulting in differences in numbers of follow-up imaging. These differences in follow-up imaging have significant impact on costs, time and radiation exposure.

To evaluate the clinical impact of the different assays, the NPV of each assay was determined. Based on a recent meta-analysis the maximum acceptable failure rate is 1.85 to 2.0% depending on the prevalence of PE [9]. This implies a minimal NPV of 98%. The NPV for patients without YEARS items with a cutoff level of 1000 ng/mL was comparable between assays (99.5–100%). It therefore appears that all assays perform equally well in patients without YEARS items in the YEARS study. This is supported by previous studies in which a D-dimer assay was used to exclude PE in low-risk patients [10,11].

In contrast to the Wells algorithm, the YEARS algorithm also applies a D-dimer assay with a cutoff level of 500 ng/mL to exclude PE in patients with a high clinical suspicion for PE (i.e., those who have ≥ 1 YEARS item). In this group the NPV varied slightly between assays (97,0–100%). According to the present post hoc analysis, no PE diagnoses in the high risk patient group were missed when using the YEARS algorithm in combination with the Liatest and the Innovance assay. In the Tinaquant assay and Vidas assay 3 PE patients were missed due to a D-dimer value below the cutoff level. Interestingly, all three patients with PE that were missed were “protocol violations” and thus were not managed according to the algorithm. In these patients a CT scan was performed at baseline despite the low D-dimer concentration. It appears that in the high risk group, the Liatest and Innovance assays performed better with respect to the NPV, although the choice for specific D-dimer assay was non-random but based on local preference with different patients presenting to the different hospitals (Table 1). A possible solution for improvement of the specificity and PPV without compromising the sensitivity and NPV could be adjustment of cutoff values per assay. However this is not desirable in clinical practice since clinicians are used to the clear and comparable cutoff values in different hospitals. Therefore further optimization of patient care could be reached by standardization of the D-dimer assays.

In the present study we found significant differences between D-dimer assays with lowest D-dimer concentrations within the Tinaquant assay group. There are several possible causes for these differences between assays. D-dimers are part of different sizes of fibrin degradation products and therefore the antigens are a diverse group of molecules. The monoclonal antibodies used in the different assays, recognize different epitopes of the antigens with their own specificity. This results

in a different reaction with high- and low-molecular-weight fibrin degradation products and therefore in a different laboratory result. Furthermore, the assay format, assay calibration standards and instrumentation varies per method used and also per analyzer and batch of reagent used [12]. Therefore, further improvement of the diagnostic properties of D-dimer tests might be reached by worldwide standardization of the assays between the diagnostic companies manufacturing them. Hence, the development of a WHO standard, however difficult, would be helpful.

Several issues warrant comment. First, this was a post-hoc analysis. Second, ideally, all patients should have been measured with all four assays. In the present analyses only 271 (7.8%) of the D-dimer results were obtained with the Vidas assay. Also baseline characteristics of the patients undergoing the D-dimer test differ significantly between the four groups, which may account for observed differences between the various assays. For example, the Vidas group has a relatively higher mean age, which might explain higher values. The Innovance group contains the least outpatients, which also might cause higher D-dimer concentrations, while the Tinaquant group consists of the least patients with reported malignancies, which might result in lower D-dimer concentrations compared to the other D-dimer groups. However, all sites applied the same criteria and patients were analyzed according to their risk for PE.

5. Conclusions

This post-hoc analysis of the YEARS study shows differences between D-dimer assays, which may point to differences in sensitivity and specificity of the different assays when used in the YEARS algorithm, and specifically, an effect on the number of patients needing follow-up imaging. These results underline the need for standardization of the D-dimer assays. In order to reach this goal, development of a WHO D-dimer standard would be a step forward as would the use of similar monoclonal antibodies in the assays provided by different diagnostic companies.

CRedit authorship contribution statement

H.M. Hamer, A.K. Stroobants, G.A.E. Ponjee and H.A. Hendriks contributed to the concept and design of the study. H.M. Hamer, A.K. Stroobants and R. Bavalia wrote the manuscript and performed the analysis. F.A. Klok, T.van der Hulle, M.V. Huisman, S. Middeldorp provided the data from the YEARS study since they were involved in the original YEARS investigators group. G.A.E. Ponjee, H.A. Hendriks, F.A. Klok, M.V. Huisman and S. Middeldorp critically revised the manuscript. All authors approved the final version of the manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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References

- [1] C.G. Santos-Gallego, J. Bayon, J.J. Badimon, Thrombi of different pathologies: implications for diagnosis and treatment, *Curr. Treat. Options Cardiovasc. Med.* 12 (2010) 274–291, <https://doi.org/10.1007/s11936-010-0075-8>.
- [2] M. Di Nisio, A. Squizzato, A.W. Rutjes, H.R. Buller, A.H. Zwinderman, P. M. Bossuyt, Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review, *J. Thromb. Haemost.* 5 (2007) 296–304, <https://doi.org/10.1111/j.1538-7836.2007.02328.x>.
- [3] C. Longstaff, D. Adcock, J.D. Olson, I. Jennings, S. Kitchen, N. Mutch, P. Meijer, E. J. Favaloro, G. Lippi, J. Thachil, Harmonisation of D-dimer - a call for action, *Thromb. Res.* 137 (2016) 219–220, <https://doi.org/10.1016/j.thromres.2015.11.031>.
- [4] P.S. Wells, D.R. Anderson, M. Rodger, I. Stiell, J.F. Dreyer, D. Barnes, M. Forgie, G. Kovacs, J. Ward, M.J. Kovacs, Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer, *Ann. Intern. Med.* 135 (2001) 98–107.
- [5] M.V. Huisman, S. Barco, S.C. Cannegieter, G. Le Gal, S.V. Konstantinides, P. H. Reitsma, M. Rodger, A. Vonk Noordegraaf, F.A. Klok, Pulmonary embolism, *Nat. Rev. Dis. Primers.* 4 (2018) 18028, <https://doi.org/10.1038/nrdp.2018.28>.
- [6] T. van der Hulle, W.Y. Cheung, S. Kooij, L.F.M. Beenen, T. van Bommel, J. van Es, L.M. Faber, G.M. Hazelaar, C. Heringhaus, H. Hofstee, M.M.C. Hovens, K.A. H. Kaasjager, R.C.J. van Klink, M. Kruip, R.F. Loeffen, A.T.A. Mairuhu, S. Middeldorp, M. Nijkeuter, L.M. van der Pol, S. Schol-Gelok, M. Ten Wolde, F. A. Klok, M.V. Huisman, group Ys, Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study, *Lancet* 390 (2017) 289–297, [https://doi.org/10.1016/S0140-6736\(17\)30885-1](https://doi.org/10.1016/S0140-6736(17)30885-1).
- [7] L.M. van der Pol, C. Tromeur, I.M. Bistervels, F. Ni Ainle, T. van Bommel, L. Bertoletti, F. Couturaud, Y.P.A. van Dooren, A. Elias, L.M. Faber, H.M.A. Hofstee, T. van der Hulle, M. Kruip, M. Maignan, A.T.A. Mairuhu, S. Middeldorp, M. Nijkeuter, P.M. Roy, O. Sanchez, J. Schmidt, M. Ten Wolde, F.A. Klok, M. V. Huisman, Study I. Artemis, Pregnancy-adapted YEARS algorithm for diagnosis of suspected pulmonary embolism, *N. Engl. J. Med.* 380 (2019) 1139–1149, <https://doi.org/10.1056/NEJMoa1813865>.
- [8] M. Righini, J. Van Es, P.L. Den Exter, P.M. Roy, F. Verschuren, A. Ghuyens, O. T. Rutschmann, O. Sanchez, M. Jaffrelot, A. Trinh-Duc, C. Le Gall, F. Moustafa, A. Principe, A.A. Van Houten, M. Ten Wolde, R.A. Douma, G. Hazelaar, P. M. Erkens, K.W. Van Kralingen, M.J. Grootenboers, M.F. Durian, Y.W. Cheung, G. Meyer, H. Bounameaux, M.V. Huisman, P.W. Kamphuisen, G. Le Gal, Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study, *JAMA.* 311 (2014) 1117–1124, <https://doi.org/10.1001/jama.2014.2135>.
- [9] C.E.A. Dronkers, T. van der Hulle, G. Le Gal, P.A. Kyrle, M.V. Huisman, S. C. Cannegieter, F.A. Klok, Subcommittee on P, diagnostic variables in thrombotic D. Towards a tailored diagnostic standard for future diagnostic studies in pulmonary embolism: communication from the SSC of the ISTH, *J. Thromb. Haemost.* 15 (2017) 1040–1043, <https://doi.org/10.1111/jth.13654>.
- [10] W. Ghanima, P.M. Sandset, Validation of a new D-dimer microparticle enzyme immunoassay (AxSYM D-dimer) in patients with suspected pulmonary embolism (PE), *Thromb. Res.* 120 (2007) 471–476, <https://doi.org/10.1016/j.thromres.2006.11.005>.
- [11] L.D. Sanchez, D.C. McGillicuddy, K.A. Volz, S.L. Fan, N. Joyce, G.L. Horowitz, Effect of two different FDA-approved D-dimer assays on resource utilization in the emergency department, *Acad. Emerg. Med.* 18 (2011) 317–321, <https://doi.org/10.1111/j.1553-2712.2010.00973.x>.
- [12] S.S. Adam, N.S. Key, C.S. Greenberg, D-dimer antigen: current concepts and future prospects, *Blood.* 113 (2009) 2878–2887, <https://doi.org/10.1182/blood-2008-06-165845>.