Thrombosis Research 174 (2019) 13–15

Contents lists available at ScienceDirect

Thrombosis Research

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

Letter to the Editor-in-Chief

Low D-dimer levels in sepsis: Good or bad?

Disseminated intravascular coagulation (DIC) is found in 25–50% of patients with sepsis and may contribute to organ failure, thereby greatly increasing the risk of death [1,2]. The international Society of Thrombosis and Haemostasis (ISTH) has proposed a scoring system to facilitate the diagnosis of DIC [3], which is based on four simple laboratory tests, namely prolongation of prothrombin time (PT, score 0-1-2), fibrinogen drop (score 0-1), thrombocytopenia (score 0-1-2) and increase of a fibrin-related product, such as soluble fibrin monomers (SFM), D-dimer (DD) or fibrin(ogen) degradation products (FDP) (score 0-2-3). A score ≥5 is considered compatible with overt DIC, meaning that the fibrin-related product has the greatest impact on DIC diagnosis, being the only test that may score 3 in case of strong positivity. DD is the most used fibrin-related marker for the diagnosis of DIC because DD assays are widely available, simple and rapid [4]. Moreover, elevated DD per se has been reported to be associated with a greater incidence of death in septic patients [5].

DD is a fibrin breakdown product that arises from three reactions: 1) fibrinogen to fibrin conversion by thrombin, 2) fibrin cross-linking by activated factor XIII and 3) fibrin degradation by plasmin [6]. This implies that the levels of circulating DD depend on both coagulation and fibrinolysis activation. Sepsis is characterized by a marked inhibition of fibrinolysis due to several mechanisms, which include increased plasminogen activator inhibitor 1 (PAI-1), activation of thrombin activatable fibrinolysis inhibitor (TAFI) and increased plasma levels of nuclear products such as cell-free DNA and histones [7,8]. It is likely, therefore, that the levels of DD in septic patients might not properly mirror the extent of fibrin formation during DIC, possibly leading to false negative results. In a recent study on septic patients selected from the ALBIOS trial [8], we confirmed the presence of markedly elevated DD, whose median levels on day 1 after admission amounted to about 4000 ng/ml. However, by Cox analysis we found that higher levels of DD (tested as continuous variable) were associated with a reduced risk of death [8]. In DIC score calculation, DD is categorized as normal, moderately increased and markedly increased, and given a score of 0, 2, and 3, respectively [3]. We re-evaluated our data by dividing our patients in three groups using cut-off levels of DD similar to those previously reported and validated [9]: 1) no increase (< 500 ng/ml), 2) moderate increase (500–4000 ng/ml), and 3) marked increase (> 4000 ng/ml). A detailed description of patients' selection, blood sampling and processing, and assay methods is reported elsewhere [8]. The most relevant characteristics of patients grouped by DD category are summarized in Table 1. Patients without DD increase did not differ from the other two groups with respect to age, sex, SAPSII (Simplified Acute Physiology Score II) and prevalence of thrombocytopenia or shock. Only SOFA (Sequential Organ Failure Assessment) score was slightly lower in patients with moderate DD increase. Thus, considering these well-established prognostic factors, the three groups had a fairly similar illness severity. Still, by Kaplan-Meier analysis (Fig. 1), patients without DD increase had a mortality rate much greater than that of patients with moderate and marked DD increase ($P = 0.0003$). In fact, 6 out of 7 patients without DD increase (85.7%) died within 12 days, a time interval at which the death rate of the other two groups was about 20%. Although we missed PT values and fibrinogen levels, we can safely state that patients with DD levels within the "normal" range are unlikely to be diagnosed with overt DIC (Table 1). Actually, overt DIC could be excluded with certainty in 5 out of 7 patients with normal DD because their platelet count was $> 50 \times 10^3/\mu L$, meaning that maximum DIC score achievable was 4. On the other hand, overt DIC was likely in patients with marked DD increase, and certain in those who also had severe thrombocytopenia ($n = 47$), whose minimum score was 5 (Table 1). Concerning the mechanism behind the very high mortality in patients with normal DD, we hypothesize that these patients had a form of DIC in which the inhibition of fibrinolysis was exceptionally strong such that it prevented fibrin degradation and DD rise. This hypothesis harmonizes with the finding that the circulating levels of plasmin-antiplasmin complex (PAP), which is a reliable marker of in vivo plasmin formation, were lower in patients with "normal" DD as compared to patients with moderate or marked DD increase, whereas PAI-1 levels were higher (Table 1). Intriguingly, however, while the levels of total TAFI were fairly similar in the three groups, the levels of activated TAFI (TAFIa) and its inactive derivative TAFIai (collectively referred to as TAFIa/ai), which reflect in vivo TAFI activation [10], were highest in patients with marked DD increase (Table 1). One possible explanation for this finding is that TAFI activation in the latter group was principally driven by plasmin rather than by thrombin, as hypothesized in patients under warfarin treatment, who displayed higher levels of circulating TAFIa/ai despite the marked reduction in thrombin generation [11].

To our knowledge, this is the first report showing that patients with proven sepsis and DD level within the normal range had the greatest mortality rate. Thus, whatever the mechanism(s) beneath the lack of DD increase in such patients, it can be suggested that the use of DD for DIC diagnosis and risk stratification in severe sepsis may be misleading.

One significant limitation of our study is the small size of the group with no DD increase, which was expected because the number of patients with DD levels in the "normal" range is usually very low in proven sepsis [12]. However, the difference in survival compared to the other DD groups was so striking that a type 1 error is very unlikely.

In conclusion, if our hypothesis of an unusually strong inhibition of fibrinolysis will be confirmed by larger studies, the small group of septic patients with low DD and very high mortality risk would very likely benefit from a targeted therapy aimed at controlling clotting activation and/or promoting fibrinolysis, such as, for example, recombinant soluble thrombomodulin [13], whose efficacy was shown to increase with increasing baseline risk [14]. Moreover, our findings caution against the widely held assumption that high DD is associated with increased mortality in sepsis, a condition in which the balance between fibrin formation and fibrin breakdown is frequently tilted to

https://doi.org/10.1016/j.thromres.2018.12.003
Received 23 August 2018; Received in revised form 24 October 2018; Accepted 3 December 2018
Available online 05 December 2018

Table 1
Characteristics of patients grouped according to DD category.

Variable	DD category			*P*
	No increase (n = 7)	Moderate increase (n = 122)	Marked increase (n = 142)	
Age (y)	76 (74–79)	72 (62–78)	70 (61–77)	0.23
Female sex (%)	57	45	43	0.75
SOFA score	9 (5.8–12.8)	8 (5–10)	9 (7–11)	0.03
SAPSII	49 (35–66)	48 (38–61)	53 (41–62)	0.48
Shock (%)	71.4	58.2	64.6	0.49
Thrombocytopenic (%)*	28.6	23.1	31.2	0.35
Overt DIC thrombocytopenic	Unlikely	Very likely	Confirmed	–
(DIC min-max score, n)†	(2–5, n = 2)	(4–7, n = 29)	(5–8, n = 47)	
Overt DIC non-thrombocytopenic‡	Excluded	Possible	Likely	–
(DIC min-max score, n)†	(0–4, n = 5)	(2–6, n = 92)	(3–7, n = 94)	
PAP (ng/ml)	470 (234–1126)	1223 (611–2387)	2196 (1359–5258)	< 0.0001
PAI-1 (ng/ml)	500 (232–525)	148 (83–314)	192 (114–443)	0.006
TAFI (%)	53.3 (47–71)	57.9 (33–91)	51.2 (30–77)	0.28
TAFIa/ai (ng/ml)	60.5 (32–71)	51.8 (37–73)	79.2 (56–117)	< 0.0001

Data represent median (interquartile range) or percent. Assays were performed on day 1 after admission to ICU. *P* values derived by Kruskal-Wallis or Chi-squared test. *, Platelets $< 50 * 10^3$/μl. †, Minimum DIC score assuming that both PT and fibrinogen scored 0; maximum DIC score assuming that PT and fibrinogen scored 2 and 1, respectively. ‡, Non-thrombocytopenic included also patients with platelet count between 50 and $100 * 10^3$/μl (platelet score 1). Platelet count was not available in 2 patients. See text for additional details.

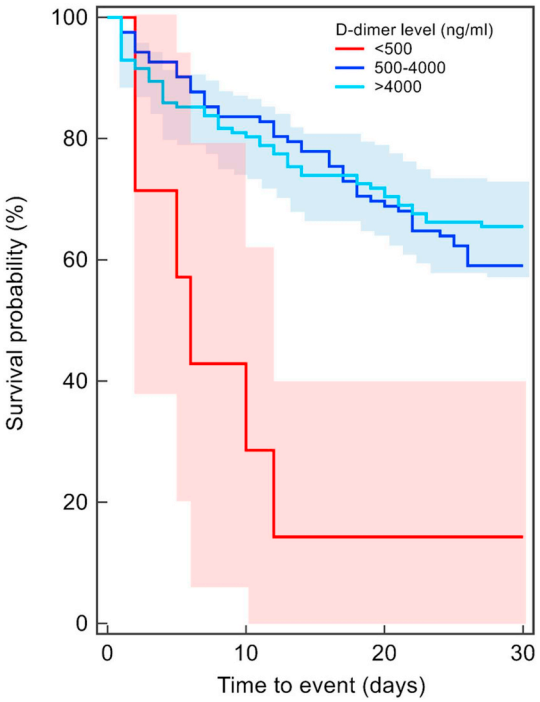

Fig. 1. Kaplan-Meier Survival curves of septic patients grouped according to DD category. Shaded areas represent 95% confidence intervals (CI). For the sake of clarity, CI of moderate DD increase group was omitted. Log-rank test $P = 0.0003$.

the left. Most likely, as also suggested by others [15], a more genuine marker of fibrin formation, such as SFM, or even better a combination of DD and SFM, which provides a broader picture of the coagulation-fibrinolysis balance, seems to be more suitable for DIC diagnosis and risk stratification in patients with proven sepsis.

Conflict of interest disclosure

The authors declare that they have no conflict of interests.

Funding

MC received support from Università degli Studi di Bari Aldo Moro, Italy. LG, PC, RL, and SM received support from the Italian Medicines Agency (AIFA, grant FARM6JS3R5, 2006) and the Italian Ministry of Health (Ricerca Finalizzata 2011–2012, grant RF-2011-02348358).

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