INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH

IJCMPR

Available Online at http://www.journalcmpr.com

RESEARCH ARTICLE

RELATIONSHIP BETWEEN COAGULATION TESTS ABNORMALITIES AND OUTCOME IN ICU PATIENTS: A PROSPECTIVE COHORT STUDY

Ahlem Trifi[1]., Sami Abdellatif[1]., Montassar Bouzidi[1]., Hela Baccouche[2]., Foued Daly[1]., Rochdi Nasri[1]., Khaoula Mahjoub[1]., Neila Ben Romdhane[2] and Salah Ben Lakhal[1]

[1]Medical intensive Care Unit. University Hospital Center of La Rabta, Tunis
[2]Haematology Department. University Hospital Center of La Rabta, Tunis

ARTICLE INFO

Article History:

Received 24th, July, 2016,
Received in revised form 1st, August, 2016, Accepted 6th, September, 2016, Published online 21st, October, 2016

Key words:

Thrombocytopenia, Prolonged Clotting Times, Disseminated Intravascular Coagulation, Bleeding, Ischemia, Mortality, Usefulness

ABSTRACT

Purpose: to examine the impact of coagulation abnormalities on survival and analyze the performance of routine coagulation tests to predict clinical outcomes in intention to improve the survival in intensive care unit (ICU) patients by the using of routine coagulation tests.
Methods: a prospective double cohort study during 10 months. All patients admitted were included. Those with congenital coagulation disorder and curative anticoagulation were excluded. Daily monitoring of blood count and standard coagulation tests were performed. Kaplan-Meier curves, Logistic regression and ROC curves were used for analysing the impact of coagulation disorders and assessment of usefulness of routine coagulation tests.
Results: Mortality was significantly higher in the coagulation disorders group (55% vs 14%, p <0.001) and disseminated intravascular coagulation (DIC) was an independent factor related to mortality (OR=3.37, CI95% [1.85-4.90], p=0.012). The leading cause of mortality was ischemic or bleeding complications (56%). We found that prolonged clotting time had significant sensitivity and negative predictive value (NPV) (94.7% and 98% respectively) to predict ischemia, whereas thrombocytopenia had a NPV at 91.4% to predict bleeding and hyper D dimer/hypofibrinogen have specificity at 91.6% to predict bleeding. An ISTH score > 3.5 was significantly related to death with a specificity of 98%, a PPV of 90% and a robust likelihood ratios: LR+=17 and LR-=0.66.
Conclusion: coagulation disorders were significantly associated to mortality. The conventional coagulation tests can be useful for the early detection and management of ischemic/bleeding events.

INTRODUCTION

Background: coagulation disorder is "a condition in which the blood's performance to clot is impaired". Because of the complexity of the haemostatic pathways, this term include also the thrombotic states [1,2]. Thrombocytopenia and prolonged clotting times are the most common biological profiles reported in critically ill patients. Several studies in surgical and trauma units reported an unfavourable correlation between coagulopathy and outcome [3-5]. The death of a patient with coagulopathy is usually caused by a severe hemorrhagic or thrombotic incident. Yet, the clinical significance of the abnormalities of standard coagulation tests remains poorly understood. Indeed, the tendency of bleeding or ischemic event cannot be clearly known in advance by the standard laboratory investigations. Standard laboratory tests of blood coagulation provide only partial diagnostic information. Important coagulation defects, e.g., reduced clot stability, platelet dysfunction, or hyperfibrinolysis, remain undetected. Therefore, point-of-care diagnostics (thromboelastography: TEG techniques) are increasingly being used for rapid specific testing of haemostatic function. Algorithm-based hemotherapy, including TEG techniques, reliably corrects coagulopathy, but may also have the potential to reduce blood loss, transfusion requirements and risk of transfusion-related adverse events, prevent thromboembolic events, and save costs [6, 7]. Unfortunately, these techniques exploring the blood viscosity are not used in several laboratories such in our context. Thus, it seems to be interesting to evaluate the performance of the routine coagulation tests to predict hemorrhagic and/or ischemic events. Perhaps, the application of these parameters becomes, not only interesting for biological monitoring, but also to be used in the aim to improve care and management and therefore the survival in the intensive care unit (ICU).

Herein, we aimed to assess the impact of coagulation abnormalities on survival and to analyse the performance of routine coagulation tests to predict clinical outcomes in intention to improve the survival ICU patients by the using of routine coagulation tests.

PATIENTS AND METHODS

Study design and patients: a prospective observational and analytical cohort study performed in a medical ICU with the collaboration of a haematological laboratory over 10 months from July 2014 to April 2015. Were eligible, all patients admitted during the study period. Exclusion criteria were: an ICU stay <72 hours, congenital deficiency of coagulation proteins (protein S, C and antithrombin) and curative anticoagulation. Included patients were analysed according to the nature of haemostatic disorders: thrombocytopenia (TCP), prolonged clotting times (PCT), combined disorders (TCP and PCT), others (hyper D dimers, hypofibrinogen...) and those that not presented haemostatic disorders.

Definitions: a coagulation disorder was considered when haematological abnormality occurred in the blood count such thrombocytopenia or in the standard haemostatic analysis such prolonged clotting times, hypofibrinigen or hyper Ddimer. Thrombocytopenia was defined as a platelet count $<150x10^9$/l or a decrease in platelet count ≥ 50% from the ICU admission value [8]. The nadir platelet count was defined as the lowest platelet count recorded during the ICU stay. It was classified as minimal thrombocytopenia when the platelet nadir was between $150x10^9$/l and $100x10^9$/l, moderate if it was between $100x10^9$/l and $50x10^9$/l and severe if it was $<50x10^9$/l.

Prolonged prothrombin time (PT in seconds) was defined as an international normalized ratio: INR (thromboplastin patient divided by thromboplastin control ratio) > 1.5 or a prothrombin in percentage <50%. Prolonged activated partial thromboplastin time (aPTT) was defined as a ratio patient / control > 1.5. Were considered as hypofibrinogen and elevated D dimer when fibrinogen dosage was less than 2 g/l and D dimer higher than 500 µg/l.

The diagnosis of DIC was based on the International Society for Thrombosis and Hemostasis (ISTH) scoring system comprising 4 routine laboratory tests (platelet count, PT, fibrinogen and D dimers) and DIC was considered when this score was higher than 5 points [9].

Data collection: were recorded: general characteristics including age, gender, pre-existing underlying diseases, primary reason for ICU admission and severity of illness as assessed by the Simplified Acute Physiology Score 2 (SAPS 2) and the Sequential Organ Failure Assessment (SOFA) score, daily clinical examination (mainly bleeding or thromboembolic events) in addition to laboratory data upon ICU admission and daily: hematologic tests (platelet count, PT, aPTT, fibrinogen and D dimers), the length of stay in ICU, 30-day vital status and cause of death. Patients were followed during 30 days.

Laboratory methods: Blood samples were obtained from patients admitted to the ICU for use in the measurement of platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), D-dimers, fibrinogen, fibrin degradation products (FDPs), and DIC scores. Blood samples were taken following admission to the ICU, daily and when a clinical event such bleeding or thrombosis occurred. Blood samples for blood count were collected into commercially available Ethylene diamine tetra-Acetic (EDTA) tubes. The tubes containing sodium-citrate were used to determine PT, aPTT, D-dimers and FDPs. Samples were centrifuged for routine testing, and analysis was performed within 1 hour after sampling. aPTT, PT and fibrinogen were performed by the coagulometric method using respectively the following reagents Pathromtin SL®, Innovin® and Dade Thrombin®. D dimers were determined by the immunologic method using Innovance Ddimer® reagent.

Statistical analyses: The continuous and normally distributed quantitative variables were expressed as mean and standard deviation (SD) and compared using the Student t test. Quantitative variables with non-Gaussian distribution were expressed as median and interquartile ranges (IQR) and compared using the Mann-Whitney U test. The qualitative variables were expressed as percentages and compared using the Chi 2 test or Fisher exact test as appropriate. The measures of association between haemostatic disorders and mortality were expressed by the odds ratio using the logistic regression (stepwise regression model). The factors with a significance < 0.2 in the univariate analysis were selected in the multivariate analysis. The performance of routine coagulation tests to predict bleeding or haemostatic event was assessed by the area under the curve (AUC) using the Receiver operating characteristic (ROC) curves. Survival analysis was processed by the Kaplan-Meier survival curves and compared by the log-rank test. All tests were two-sided, and a p value <0.05 was considered to indicate statistical significance. The IBM SPSS Statistics 20 software was used for statistical analysis.

Ethics statement: This study was approved by our ethics committee and that comply with the principles of the Declaration of Helsinki.

Table 1 Patient's demographic and clinical characteristics

Groups study	With Haemostatic disorders (n=86)	Without Haemostatic disorders (n=73)	P value
Age (years), mean ± SD	48±18	43±20	0.1
Sex-ratio (M/F)	41/45 (0.91)	44/29 (1.51)	0.17
SAPS II, mean ± SD	35±16	28±14	**0.007**
SOFA, mean ± SD	6.1±4.4	5.2±3.4	0.13
Admission reason, n (%):			
- Acute respiratory failure	27 (31%)	21 (28%)	0.73
- Septic shock	17 (20%)	5 (7%)	**0.022**
- Cardiogenic shock	6 (7%)	2 (3%)	0.29
- Coma :			
o Traumatic	5 (6%)	4 (5.4%)	1
o Non Traumatic	19 (22%)	18 (24.6%)	0.63
o Metabolic cause	5 (6%)	16 (22%)	**0.004**
o Others	6 (8%)	7 (10%)	0.24
Co-morbidities n (%):	32 (37%)	14 (19%)	**0.014**
- Systemic disease	6 (6.7%)	2 (3%)	0.09
- -Cardiac failure	5 (6%)	1(1.4%)	-
- -neoplasy	3 (3.6%)	2 (3%)	-
- -cerebral vascular accident	4 (5%)	0	-
- -Hepatopathy	3 (3.6%)	0	-
- -Immunodeficiency	3 (3.6%)	1(1.4%)	-
- -chronic intestinal diseases	3 (3%)	1(1.4%)	-
- -Surrenalian failure	1 (1.2%)	0	-
- -Dysthyroidy	2 (2.4%)	1(1.4%)	-
- -Splenectomy	1(1.2%)	0	-
- -Diabetis	2 (2.4%)	5 (7%)	**0.07**
- -Arterial Hypertension	4 (4.3%)	2 (3%)	-
- -Renal failure	2 (2.4%)	1(1.4%)	-
Sepsis (at admission or during ICU stay (%))	70 (81%)	36 (49%)	**<0.001**
ICU length of stay (d), median (IQR)	15 (9-22)	8 (5-10)	**0.04**
Mortality, n (%)	48 (55%)	10 (14%)	**<0.001**
		-	-

SD: standard deviation, IQR: inter-quartile range, LOS: length of stay, SAPS II: simplified acute physiology score II, ICU: intensive care unit, SOFA: Sepsis-related Organ Failure Assessment, TCP: thrombocytopenia, PCT: prolonged clotting times, n*: number of abnormality test

Due to the absence of interventional nature of the study, informed consent was not required.

RESULTS

Baseline characteristics: Among the 159 patients included during the study period, 86 (54%) have presented haemostatic disorder (HD). Patients that presented haemostatic disorder have a higher SAPS II **(**simplified acute physiology II) score, demographic characteristics were comparable. Besides the acute respiratory failure, the main reason of admission of all patients, septic shock was more frequent in HD+ group versus metabolic disorders in HD-group. The underlying diseases were more common with HD+ group (37% vs 19%, p = 0.014). The most reported co morbidities were: autoimmune diseases, heart failure and a pre-existing brain-vascular accident. Occurrence of sepsis (at admission or during hospitalization) was more described with HD+ group.

Identified coagulation tests abnormalities were: TCP (isolated: 14/53 and associated with PCT: 39/53), PCT (isolated: 33/72 and associated with TCP/ 39/72), combined disorder: 39 cases including 20 cases of DIC. Hyper Dimer (n = 20) and Hypofirinogen (n = 20). Table 1 shows the characteristics of all included patients as well as the identified coagulation tests abnormalities.

Impact of coagulation tests abnormalities on outcome

The ischemic and bleeding events were significantly increased in group with coagulation tests abnormalities (5.5% vs 39.5%, p<0.0001 and 6.8% vs 27%, p=0.001 respectively). Among this group, ischemic events were more frequent than bleeding events [n=34 (39.5%) versus n=23 (27%)]. The most common events were pulmonary embolism (9/34) and brain haemorrhage (6/23). Details of clinical events depending on the coagulation disorder are outlined in Table 2.

Overall, the ICU-length of stay was longer with HD+ group [15 (9-22) versus 8 (5-10) days, p=0.04]. The more long stay among the 4 HD subgroups was noted with the PCT disorder (Figure 1).

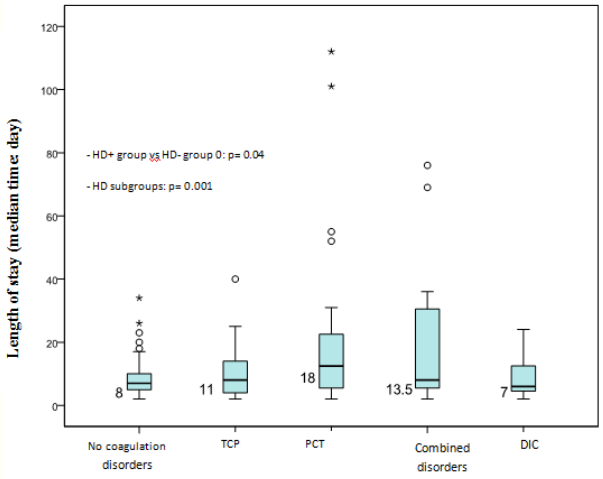

Figure 1 ICU-Length of stay of the study groups

Overall, the length of stay (LOS) was more prolonged with the group with coagulation disorders [15 d (9-22) versus 8 d (5-10), p = 0.04]. The higher LOS was observed with prolonged clotting times and the shortened with DIC group with a significant difference (p=0.001). *HD: haemostatic disorders, LOS: length of stay, TCP: thrombocytopenia, PCT: prolonged clotting times, DIC: disseminated intravascular coagulation.*

Overall, the 28-day all- cause mortality was significantly higher in the coagulation disorders group (55% versus 14%, p <0.001). Survival analysis showed that the median survival time was shortened by 6, 7, 13 and 16 days in thrombocytopenia, prolonged clotting times, combined disorder and DIC groups respectively compared to the control group. The survival curves at 28 days of both groups are outlined in Figure 2.

Table 2 Clinical events according to the type of coagulation disorder

	Isolated TCP, n=14 (17%)	Isolated PCT, n=33 (38%)	Combined disorders, n=19 (22%)	DIC, n=20 (23%)	Total,
Ischemic events: (n/total of 34)					
-Pulmonary embolism: 9	0	3	4	2	9
-Deep venous thrombosis: 8	0	4	2	2	8
-Coronary ischemia: 7	0	2	3	2	7
-Cerebral Thrombophlebitis: 5	0	2	2	1	5
-Ischemic stroke: 4	1	2	1	0	4
-Acute limb ischemia: 1	0	1	0	0	1
Total of ischemic events	**1**	**14**	**12**	**7**	**34 (39.5%)**
Bleeding events: (n/total of 23)					
-Brain haemorrhage: 6	1	1	2	2	6
-Haemoptysis: 5	0	1	1	3	5
-Gastrointestinal: 4	1	1	1	1	4
-At Catheter care:4	1	0	2	1	4
-At Bedsores Care: 3	0	1	0	2	3
-Vascular Purpura: 1	0	0	1	0	1
Total of Bleeding events	3	4	7	9	**23 (27%)**
No clinical event	10	15	0	4	**29 (33.5%)**
Total	14	33	19	20	**86 (100%)**

Values are expressed as n times of occurrence of the clinical event in according to the coagulation disorder
TCP: thrombocytopenia, PCT: prolonged clotting times, DIC: disseminated intravascular coagulation

The death was related to the ischemic complications in 17/34 (50%) with mainly a refractory cardiogenic shock complicating severe pulmonary embolism and Coronary ischemia.

Regarding the bleeding complications, the death was related to 10/23 (43.5%) of cases by a refractory hemorrhagic shock.

Multivariate analysis demonstrated that coagulation abnormalities (all types of disorders confounded) were significantly related to mortality (OR: 2.12, CI95% [1.29-2.85], p <0.001). But, if each type of disorder was analysed, DIC was an independent factor associated to mortality. Others factors were also significantly related to mortality: sepsis

whether at admission or during ICU hospitalisation and co-morbidities (Table 3).

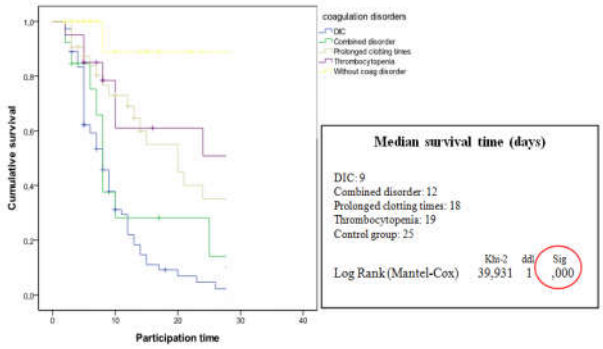

Figure 2 Survival analysis of study groups

The probability of survival at 30 days was significantly reduced in DIC and combined disorders groups compared to isolated anomalies and the group without bleeding disorders with p value < 10^{-3}. DIC: disseminated intravascular coagulation

Table 3 Factors associated with mortality by stepwise logistic regression

Variables	Univariate analysis		Multivariate analysis	
	OR [95%CI]	P value	OR [95%CI]	P value
Coagulation disorders*	2.86 [1.99-3.48]	<0.001	2.12 [1.29-2.85]	**<0.001**
Thrombocytopenia	1.8 [1.31-2.46]	0.01	1.01[0.82-2.04]	0.39
Prolonged time clotting	1.27 [0.98-1.86]	0.08	1.46 [0.77-1.95]	0.28
DIC	7.62 [2.04-28.49]	<0.0001	3.37 [1.85-4.90]	**0.012**
Age (>50 vs < 50 years)	1.27 [0.92-2.06]	0.08	1.11 [0.68-1.88]	0.25
Males (vs female)	1.24 [0.69-1.77]	0.5	-	-
SAPS II (> vs< 30)	1.45 [1.01-2.14]	0.062	1.04 [0.87-1.25]	0.23
Co-morbidities	2.34 [1.72-2.87]	0.01	1.88 (1.20-2.45)	**0.017**
Presence of sepsis	1.88 [1.60-1.97]	0.02	1.42 [1.20-1.67]	**0.024**
Mechanical ventilation	1.36 (0.77-2.13)	0.1	1.18 (0.92-1.54)	0.15

SAPS II: simplified acute physiology score, CI: confidence interval; OR: odds ratio, DIC: disseminated intravascular coagulation, *all confounded coagulation abnormalities

The leading cause of mortality in patients with coagulation disorders [n=48 (55%)] was the ischemic and / or bleeding complications [27/48 (56%)]. Elsewhere, death was secondary to multi organ failure syndrome of various origins mainly a septic shock in 37.5%.

DIC and mortality: 20 patients of the combined disorder group have an ISTH score ≥ 5 and therefore they were identified as having DIC. 18 died among the DIC subgroup at a median time of 5 days after diagnosis of DIC.

It has been revealed that the occurrence of DIC was an independent factor associated to mortality (OR=3.37, CI 95% [1.85-4.90], p=0.012). Regarding the performance of the ISTH score to predict mortality, we showed that when the ISTH score exceeded a value of 3.5, the risk of death increased with a specificity of 98%, a PPV of 90% and especially a robust likelihood ratios: LR+=17 and LR-=0.66 (figure 3).

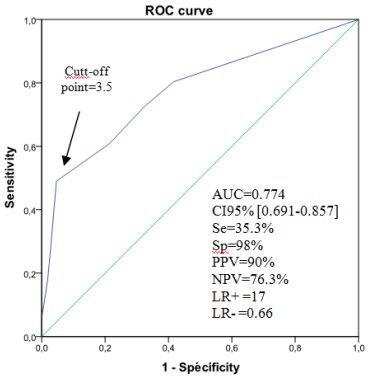

Figure 3 Performance of the ISTH score on mortality

The ROC curve analysing the performance of ISTH score to predict mortality showed that when the ISTH score exceeded a value of 3.5, the risk of death was increased with a specificity of 98%, a PPV of 90% and especially a robust likelihood ratios: LR+=17 and LR-=0.66. *AUC: area under the curve, CI: confidence interval, Se: sensitivity, Sp: specificity, PPV: positive predictive value, NPV: negative predictive value, LR+:* positive *likelihood ratio, LR-:* negative *likelihood ratio.*

Usefulness of coagulation tests abnormalities to predict clinical events

The usefulness of coagulation tests differed according to the tendency of blood impairment: hyper coagulation thus ischemic complication or hyperfibrinolysis resulting in bleeding event. Indeed, thrombocytopenia had a significant negative value to predict a bleeding (NPV=91.4%). While in ischemic event, this test was less contributory. Regarding the performance of prolonged clotting times, it was better to predict ischemic than bleeding event with significant sensitivity and NPV (94.7% and 98% respectively). The combination of these two tests abnormalities did not do better than each separate test. Hyper D dimer and hypofibrinogen had good specificity to predict bleeding (91.6%). All the measurements of the performance of routine coagulation tests to predict ischemic/bleeding event were outlined in table 4.

DISCUSSION

Coagulation abnormalities occurred in 54% among 159 medical ICU patients recorded in our prospective cohort.

Table 4 Performance of routine coagulation tests to predict ischemic/bleeding event

	Bleeding event					Ischemic event				
Coagulation tests	**AUC [CI 95%] p value**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**AUC, [CI 95%], p value**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Thrombocytopenia	0.706 [0.596-0.815] 0.001	67.9%	73.3%	35.2%	91.4%	0.657 [0.554-0.760] 0.004	57.9%	73.6%	41%	85%
Prolonged clotting times	0.659 [0.549-0.768] 0.008	71.4%	60.3%	28%	91%	0.825 [0.554-0.760] $<10^{-3}$	94.7%	70.2%	50%	98%
Thrombocytopenia + Prolonged clotting times	0.641 [0.520-0.762] 0.02	46.4%	82%	35%	87.7%	0.676 [0.570-0.781] 0.001	50%	85.1%	51.3%	84.5%
Elevated D dimers	0.619 [0.493-0.744] 0.049	33%	91.6%	45%	86.4%	0.538 [0.430-0.647] 0.47	18.4%	89.3%	35%	78%
Hypofibrinigen	0.619 [0.493-0.744] 0.049	32.1%	91.6%	45%	86.4%	0.538 [0.430-0.647] 0.47	18.4%	89.3%	35%	77.7%

AUC: area under the curve, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value

The most identified disorders was prolonged clotting times and thrombocytopenia or combined. Coagulation disorders have affected several points of evolution: occurrence of ischemic or bleeding events, prolongation of ICU- length of stay, higher mortality and limitation of survival time.

Multivariate analysis showed that coagulation disorder with mainly the DIC was an independent factor associated to mortality. The major cause of death in patients with coagulation disorders was the ischemic and / or bleeding complications (56%). This last finding prompted to analyse the performance of routine coagulation to predict ischemic and / or bleeding. It was revealed that thrombocytopenia had a NPV at 91.4% to predict bleeding complication whereas PCT had significant sensitivity and NPV (94.7% and 98% respectively) to predict ischemic event. Hyper D dimer and hypofibrinogen can predict bleeding complication with specificity at 91.6%. Furthermore, an ISTH score >3.5 was an excellent parameter to predict mortality.

The incidence and prevalence vary according to the type of disorder and the studied population. Our incidence of thrombocytopenia at 34% (53/159) is comparable to those reported by the US-European literature at 35% to 47% [10-12] and Korean studies at 37.1% [13]. Higher incidences were reported in surgery – trauma [14, 15]. The prolonged coagulation times such as PT or its Standardized Expression international normalized ratio (INR) and aPTT occurs in 14-28% of ICU patients [16]. In our series, that was higher than reported in literature: 45.3% (as isolated or integrated in mixed disorders: 72/159). The thrombo-embolic complications were more common than bleeding events with this type of disorder which confirms the hypothesis that the clotting times test does not adequately explored in vivo coagulation [17].

It has been reported that the occurrence of coagulation disorders is related with a significant morbidity and mortality [5, 18-20]. Our results adhered to the previous reviews on the unfavourable impact of these disorders: extension of ICU-stay, increasing mortality (55% versus 14%, $p < 0.001$) and limitation of survival time (18 versus 25 days, $p = 0.009$). The ICU-stay was longer with PCT subgroup (18 days). Indeed, with this subgroup, the thrombotic complications were predominant causing visceral ischemia such pulmonary embolism, stroke etc.... which increase critical care management and as a result the stay length.

Regardless of the type of disorder, coagulation test abnormalities were an independent predictor of mortality in our series (OR= 2.12, CI95% [1.29-2.85]). In various studies, thrombocytopenia is significantly associated to mortality in the ICU (OR at 1.9 to 4.2) [1, 16, 21]. High rates of mortality at 39% and 37% have been reported in thrombocytopenic patients [13, 21]. Also, both a low nadir platelet count and a large fall of platelet count predict a poor vital outcome in adult ICU patients [21].

In light of previous findings revealing high rates of mortality with mainly the relationship between ischemic/bleeding events and mortality and in the other hand the unavailability of the viscoelastic methods (TEG) in several units; it seems interesting to assess the performance of conventional coagulation tests to predict clinical events. Indeed, The TEG is increasingly used in severe patients including those with DIC with a good correlation with organ dysfunction and survival [7, 22, 23]. But clinical contribution of standard coagulation tests is not as clear. Therefore, the assessment of their usefulness to detect haemostatic disorder direction (i.e hyperfibrinolysis or hypercoagulability tendencies) could guide to an early and appropriate management of clinical events and thus to improve prognosis.

Clinical relevance of thrombocytopenia is related to increased risk of bleeding. Indeed, when platelet counts $<50x10^9$/l, the risk of bleeding is 4 to 5 times higher [1, 2, 41]. However, in many pathological situations, thrombocytopenia resulted in thrombosis. This is particularly reported in the DIC and heparin induced thrombocytopenia [1, 21, 24]. Our study showed that thrombocytopenia was of modest interest to reveal thrombo-ischemic complication (sensitivity: 57% and specificity: 73%). But the valuable contribution of thrombocytopenia was its good NPV (91.4%) for bleeding events.

However and in contrast to the biological significance, ischemic events could be detected precociously by the prolonged clotting time with a sensibility at 94.7% and a NPV at 98%. But also their NPV in bleeding complication was great. The combination of these two tests abnormalities has enhanced the specificity to predict bleeding and ischemic events (82% and 85.1% respectively). Hyper D dimer and hypofibrinogen have a good specificity to detect bleeding (91.6% for both) and a less specificity value for ischemia.

The crucial interest resulting from these tests, and with the lack of TEG methods, is to abolish the therapeutic dilemma in several situations of coagulation disorders: re-establishing the antithrombotic potential in order to decelerate the procoagulant process without aggravating the risk of bleeding. It may be appropriate to adjust the medical prescription: antithrombotic or antifibrinolytic agents according to the follow up of conventional coagulation tests. For example and according to our findings we suggest to reinforce the prophylactic anticoagulant in case of prolonged clotting times.

Otherwise, recent studies have evaluated the predictive values of mortality in coagulation disorders and DIC of some parameters and scores. FDP (fibrin degradation products) were among the best predictors of mortality with a determined cutoff value at 3.3 mg/L with 87.7% of sensitivity and 47.7% of specificity [25]. The ‘'Sonoclot" analysis combined the routine coagulation tests to the viscoelastic methods (TEG) at ICU admission [26]. The "Sonoclot Analyzer" ® provide precious information about the whole process of haemostasis, including the formation of fibrin, clot retraction and fibrinolysis. So it can detect the hyperfibrinolysis or hypercoagulability tendencies. It has been shown that prolonged clotting time (>220 seconds) and a lower platelet function index (<1.4) was significantly correlated with mortality at 30 days (correlation score = 0.876, $p < 0.05$) with a specificity of 82.6% and a sensitivity of 80.5%.

The highlights of this study are firstly the further strengthen of previous background about the harmful effect of coagulation disorders in ICU patients. Secondary to revalorize the interest of routine coagulation tests in the follow up of these patients. Thus, integrating these tests in ICU monitoring might allow an early detection of ischemic/hemorrhagic accidents and help to therapeutic adjustment and consequently to improve survival. The weakness was the lack of interventional character that is necessary for our findings to confirm the usefulness of the

clinical involvement of laboratory tests. Further clinical trials according to coagulation tests data are necessary.

CONCLUSIONS

Coagulation disorders were very common in medical ICU patients causing a significant worsening of prognosis. In more than a half of patients presenting coagulation disorders and who died, the cause was ischemic or hemorrhagic complication. The monitoring of routine laboratory tests including platelet counts, time coagulation, D dimers and fibrinogen can be useful for early detection or disconfirmation of a thrombotic or hemorrhagic event. Their combination in the ISTH score was very useful in the screening of patients with high risk of death. Otherwise, the absence of thrombocytopenia helps to disprove bleeding and hypofibrinogen with hyper D dimers can predict bleeding. On the other hand prolonged clotting times is specific for an ischemic event. Hence, adjust the pro or anti coagulants therapeutic based on these tests will have certainly a beneficial effect on outcome of ICU patients.

Reference

1. Hunt BJ. Bleeding and Coagulopathies in Critical Care. *N Engl J Med*. 2014; 370(9):847-59.
2. Levi M, Sivapalaratnam S. Hemostatic abnormalities in critically ill patients: REVIEW. *Intern Emerg Med*. 2015; 10:287–96.
3. Grottke O, Fries D, Nascimento B. Perioperatively acquired disorders of coagulation. Curr Opin Anaesthesiol. 2015; 28(2):113–22.
4. Salehpour F, Bazzazi AM, Porhomayon J, Nader ND. Correlation between coagulopathy and outcome in severe head trauma in neurointensive care and trauma units. *J Crit Care*. 2011; 26(4):352-6.
5. Brohi K, Cohen MJ, Davenport RA. Acute coagulopathy of trauma: mechanism, identification and effect. Curr Opin Crit Care. 2007; 13(6):680-5.
6. Johansson PI, Stensballe J, Vindelov N, Perner A, Espersen K. Hypocoagulability, as evaluated by thrombelastography, at admission to the ICU is associated with increased 30-day mortality. Blood Coagul Fibrinolysis. 2010; 21(2):168–74.
7. Haase N, Ostrowski SR, Wetterslev J, Lange T, Moller MH, Tousi H, *et al*. Thromboelastography in patients with severe sepsis: a prospective cohort study. Intensive Care Med. 2015; 41(1):77-85.
8. Akca S, Haji MP, Medonca A, Suter PM, Levi M, VincentJL. The time course of platelet counts in critically ill patients. Crit Care Med. 2002; 30(4):753-6.
9. Levi M. Diagnosis and treatment of disseminated intravascular coagulation. *Int J Lab Hematol*. 2014; 36:228-36.
10. Strauss R, Wehler M, Mehler K, Kreutzer D, Koebnick C, Hahn EG. Thrombocytopenia in patients in the medical intensive care unit: bleeding prevalence, transfusion requirements, and outcome. Crit Care Med. 2002; 30(8):1765-71.
11. Venkata C, Kashyap R, Farmer JC, Afessa B. Thrombocytopenia in adult patients with sepsis: incidence, risk factors, and its association with clinical outcome. *J Intensive Care***.** 2013; 1(1):9.
12. Hui P, Cook DJ, Lim W, Fraser GA, Arnold DM. The frequency and clinical significance of thrombocytopenia complicating critical illness: a systematic review. Chest. 2011139(2): 271-8.
13. So YL, Eun JJ, Hee-Jin K, Kyeongman J, Sang-Won U, Won-Jung K, *et al*. The Incidence, Causes, and Prognostic Significance of New- Onset Thrombocytopenia in Intensive Care Units: A Prospective Cohort Study in a Korean Hospital. *J Korean Med Sci*. 2012; 27(11):1418-23.
14. Stephan F, Hollande J, Richard O, Cheffi A, Maier-Redelsperger M, Flahault A, *et al*. Thrombocytopenia in a surgical ICU. Chest. 1999; 115(5):1363-70.
15. Hanes SD, Quarles DA, Boucher BA. Incidence and risk factors of thrombocytopenia in critically ill trauma patients. Ann Pharmacother. 1997; 31(3):285-9.
16. Levi M, Opal SM. Coagulation abnormalities in critically ill patients. Crit Care. 2006; 10(4):222.
17. Dempfle CE, Borggrefe M. Point of care coagulation tests in critically ill patients. Semin Thromb Hemost. 2008;34(5):445–50.
18. Hart C, Spannagl M. Coagulation disorders in the intensive care station. Internist (Berl).2014; 55(5) :521-8.
19. Salehpour F, Bazzazi AM, Porhomayon J, Nader ND. Correlation between coagulopathy and outcome in severe head trauma in neurointensive care and trauma units. J Crit Care. 2011; 26(4):352-56.
20. Nardi G, Agostini V, Rondinelli B, Russo E, Bastianini B, Bini G, *et al*. Trauma-induced coagulopathy: impact of the early coagulation support protocol on blood product consumption, mortality and costs. Crit Care. 2015; 19:83.
21. Vanderschueren S, De Weerdt A, Malbrain M, Vankersschaever D, Frans E, Wilmer A, *et al*. Thrombocytopenia and prognosis in intensive care. Crit Care Med. 2000; 28(6):1871–6.
22. Meybohm P, Zacharowski K, Weber CF. Point-of-care coagulation management in intensive care medicine. Critical Care. 2013;17:218
23. Holcomb JB, Minei KM, Scerbo ML, Radwan ZA, Wade CE, Kozar RA, *et al*. Admission rapid thrombelastography can replace conventional coagulation tests in the emergency department: experience with 1974 consecutive trauma patients. Ann Surg. 2012, 256:476–486.
24. Levi M, Schultz M. Coagulopathy and platelet disorders in critically ill patients. Minerva Anestesiol. 2010;76(10):851–9.
25. Fei A, Lin Q, Liu J, Wang F, Wang H, Pan S.. The relationship between coagulation abnormality and mortality in ICU patients: a prospective, observational study. Sci Rep-UK. 2015; 5:9391.
26. Wan P, Yu M, Qian M, Tong H, Su L. Sonoclot coagulation analysis: a useful tool to predict mortality in overt disseminated intravascular coagulation. Blood Coagul Fibrinolysis. 2016; 27(1):77-83.