Journal reading

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Title

- Prognostic implication of initial coagulopathy in out-of-hospital cardiac arrest

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- Resuscitation, 2013

Introduction

- Post cardiac arrest syndrome:
  Systemic ischemic-reperfusion injury
  Global activation of coagulation system
- The International Society on Thrombosis and Hemostasis (ISTH) disseminated intravascular coagulation (DIC) score:
  To measure the severity of the coagulopathy and is used for the diagnosis of DIC

Introduction

- MODS(Multiple organ dysfunction syndrome):
  common in PCAS
- The role of coagulation process in MODS of sepsis or trauma: DIC score with significant prognostic implication.
- **Hypothesis:**
- initial DIC score in resuscitated out-of-hospital cardiac arrest (OHCA) patients correlated with early mortality rate and cardiac arrest outcomes

Objective

- To investigate the prognostic implication of early coagulopathy represented by initial DIC score in out-of-hospital cardiac arrest (OHCA).
- To describe the severity of initial coagulopathy in cardiac arrest patients using ISTH DIC score and evaluate its prognostic implication in PCAS.

ISTH DIC score

DIC Scoring System
International Society on Thrombosis and Hemostasis (ISTH)

Platelet count: > 100 0
50-100 1
< 50 2

Prolongation
PT: < 3 sec 0
> 3 sec - < 6 1
> 6 sec 2

Fibrinogen:
> 1 g/L=>100 mg/dl .. 0
< 1 g/L 1

D-Dimer – No increase 0
Moderate increase 2
Marked increase 3

Add the 4 Parameters for total score:
Plt count, PT, fibrinogen and D-Dimer

Interpretation of score:
≥ 5 – laboratory evidence consistent with overt DIC
< 5 – suggestive of non-overt/low grade DIC

Using cut off 5
93% sensitive
98% specific for DIC

Methods

- OHCA registry: retrospective study for patients with ROSC without recent use of anticoagulant
- Time: 2008/1 ~2011/12
- Patients were assessed for prehosptial factors, initial laboratory results and therapeutic hypothermia.
- Outcome variables: survival discharge, 6-month CPC and survival duration within the first week after ROSC.

Participants and data collection

- Exclusion criteria:
  1. Age <18 years
  2. Recent use of warfarin, heparin, low molecular weight heparin and intravenous thrombolytics
- Prehospital factors: sex, age, arrest location, presence of witness, bystander CPR, time to basic life support (BLS), initial rhythm

Participants and data collection

- Total of 547 OHCA patients with **292** patients achieved ROSC
- After using exclusion criteria: **273** patients
- Final: **252 patients**(92.3%) with laboratory variables available for calculation of initial DIC score

Participants and data collection

- Outcome variables:
- survival discharge, 6-month cerebral performance category (CPC) score, duration of survival within 7 days post-ROSC
- favorable long-term outcome:

  CPC score 1 or 2

  Unfavorable outcome : CPC score 3~5

Cerebral performance category score

Table 1
Patient characteristics of study population.

Sex, male, no. (%)	149 (59.1)
Age, years, mean (SD)	64.1 (17.3)
Cardiac arrest in public location, no. (%)	52 (20.6)
Witnessed cardiac arrest, no. (%)	205 (81.3)
Bystander chest compression, no. (%)	79 (31.3)
Time to first BLS, min, median (IQR)	4 (0–11)
Shockable initial rhythm, no. (%)	69 (27.4)
Prehospital ROSC, no. (%)	7 (2.8)
Cause of arrest, no. (%)	
Cardiac	91 (36.1)
Respiratory	111 (44.0)
Traumatic	53 (21.0)
Food asphyxia	18 (7.1)
Hanging	14 (5.6)
Head and neck injury	9 (3.6)
Multiple blunt or penetrating injury	5 (2.0)
Drowning	3 (1.2)
Intoxication	1 (0.4)
Therapeutic hypothermia, no. (%)	81 (32.1)
Overt DIC (DIC score ≥ 5), no. (%)	82 (32.5)
1-week survival, no. (%)	79 (31.3)
Survival discharge, no. (%)	54 (21.4)
6-month CPC 1 or 2, no. (%)	28 (11.1)

Patient characteristics according to DIC score

	DIC score 0–2 n = 55	DIC score 3 n = 67	DIC score 4 n = 48	DIC score 5 n = 59
Prehospital and demographic variables				
Sex, male, no. (%)	39 (70.9)	39 (58.2)	26 (54.2)	36 (61.0)
Age, years, mean (SD)	55.9 (18.2)	63.8 (14.8)	73.3 (13.1)	66.9 (17.1)
Cardiac arrest in public location, no. (%)	12 (21.8)	21 (31.3)	8 (16.7)	7 (11.9)
Witnessed cardiac arrest, no. (%)	38 (69.1)	57 (85.1)	41 (85.4)	47 (79.7)
Bystander chest compression, no. (%)	20 (36.4)	25 (37.3)	18 (37.5)	12 (20.3)
Time to first BLS, min, median (IQR)	2 (0–7)	6 (1–12)	4 (0–12)	5 (0–12)
Shockable initial rhythm, no. (%)	20 (37.0)	18 (26.9)	9 (18.8)	17 (29.3)
Prehospital ROSC, no. (%)	5 (9.1)	1 (1.5)	0 (0.0)	1 (1.7)
Presumed cardiac etiology, no. (%)	27 (49.1)	29 (43.3)	13 (27.1)	18 (30.5)
DIC score components				
Platelet, 10^9/L, median (IQR)	222 (175–293)	196 (159–244)	165 (137–248)	149 (106–218)
PT, seconds, median (IQR)	14 (13–15)	15 (15–17)	17 (17–19)	21 (19–24)
Fibrinogen, mg/dL, median (IQR)	305 (260–391)	380 (278–535)	315 (268–438)	137 (205–484)
D-dimer, ug/mL, median (IQR)	2.04 (0.68–3.02)	7.32 (3.14–18.77)	15.48 (4.58–20.00[a])	15.04 (7.46–20.00[a])
Other laboratory variables for adjustment				
WBC count, 10^9/L, median (IQR)	11.5 (10.2–13.3)	12.8 (10.4–15.4)	12.6 (9.1–16.1)	13.8 (9.3–18.2)
Hematocrit, %, mean (SD)	42.1 (6.0)	38.0 (7.6)	36.1 (8.8)	36.0 (9.0)
BUN, mg/dL, median (IQR)	15 (13–19)	19 (15–30)	19 (15–43)	23 (14–45)
Creatinine, mg/dL, median (IQR)	1.2 (1.0–1.4)	1.3 (1.0–1.9)	1.3 (0.9–2.7)	1.5 (1.1–2.6)
Bicarbonate, mEq/L, mean (SD)	16.7 (4.0)	14.6 (4.4)	14.2 (4.6)	12.0 (5.3)
Albumin, g/dL, mean (SD)	4.1 (0.5)	3.6 (0.7)	3.3 (0.8)	2.9 (0.7)
Bilirubin total, mg/dL, median (IQR)	0.7 (0.5–0.9)	0.6 (0.4–0.8)	0.8 (0.5–1.0)	1.0 (0.7–1.7)
CRP, mg/dL, median (IQR)	0.20 (0.20–0.30)	0.34 (0.20–4.70)	0.80 (0.20–5.26)	3.04 (0.48–11.36)
Troponin I, ng/mL (IQR)	0.04 (0.02–0.10)	0.05 (0.04–0.15)	0.05 (0.03–0.19)	0.14 (0.06–0.36)
Therapeutic hypothermia, no. (%)	26 (47.3)	28 (41.8)	12 (25.5)	14 (23.7)
Cardiac arrest outcomes, no. (%)				
1-week survival, no. (%)	35 (63.6)	23 (34.3)	10 (21.3)	10 (16.9)
Survival discharge, no. (%)	25 (45.5)	17 (25.4)	5 (10.4)	6 (10.2)
6-month CPC 1 or 2, no (%)	17 (31.5)	8 (11.9)	0 (0.0)	2 (3.4)

Statistical analysis

- Analysis of variance (ANOVA), Kruskal–Wallis, Chi-square or Fisher's exact test was performed as appropriate for comparison between groups.
- Pearson's method : correlation analysis if 2 variables involved are both interval variables and Spearman's method was used otherwise.
- Logistic regression /Cox proportional hazards model analysis: for univariable analysis

  Logistic regression: odd ratios

  Cox proportional hazard model analysis: hazard ratios

Result: Baseline characteristics

- Overt DIC feature (DIC score = or > 5):
  82/252(32.5%) patients.
- Survival discharge to home /nursing home:
  54/252 (21.4%) patients.
- Favorable long-term outcome (6-month CPC 1 or 2) :
  28/252(11.1%) patients.
- Only 3/130 (2.3%) patients with DIC score >3 achieved favorable longterm outcome.

Result

- Increased DIC score: strong risk factor for both inhospital death and unfavorable long-term outcome (6-month CPC 3–5)
- Risk for inhospital death :1.89 (95% CI,1.48–2.41) and unfavorable long-term outcome : 2.21 (95% CI, 1.60–3.05)

Result

- Backward stepwise multivariable logistic regression models were constructed using the variables with p < 0.1 in univariable analyses.
- Inhospital death:
  1.61-fold increase of risk (95% CI, 1.17–2.22)
- Unfavorable long-term outcome:
  1.84 -fold increase of risk (95% CI,1.26–2.67)

Table 3
Stepwise multivariatelogistic regression model analysis of the relationship between poor outcome and various potential prognostic factors.

	Odds ratio	p
Inhospital death		
Sex (male)	0.47 (0.21–1.06)	0.068
Age (per 1 year)	1.03 (1.00–1.06)	0.035
Time to first BLS (per 1 min)	1.06 (1.00–1.13)	0.048
Shockable initial rhythm	0.20 (0.09–0.44)	<0.001
Bicarbonate (per 1 mEq/L)	0.91 (0.83–1.00)	0.045
Therapeutic hypothermia	0.39 (0.18–0.85)	0.018
DIC score (per 1 unit)	1.61 (1.17–2.22)	0.003
Poor long-term outcome (6-month CPC ≥ 3)		
Age (per 1 year)	1.03 (1.00–1.07)	0.060
Time to first BLS (per 1 min)	1.16 (1.03–1.31)	0.017
Shockable initial rhythm	0.14 (0.05–0.40)	<0.001
Presumed cardiac etiology	0.31 (0.11–0.92)	0.034
DIC score (per 1 unit)	1.84 (1.26–2.67)	0.002

DIC score vs. long-term prognostic performance

- **Area under the ROC curve (AUC)**
- Prediction of unfavorable long-term outcome:
  0.79 (95% CI, 0.69–0.88)
- Optimal cutoff point of DIC score to predict poor outcome:
  3~4

sensitivity	specificity	PPV	NPV
57%	89.3%	97.7%	20.7%
95% CI, 50.2–63.5	95% CI, 71.8–97.6	95%CI, 93.4–99.5	95% CI, 13.8–29.0

DIC score vs. Early mortality risk

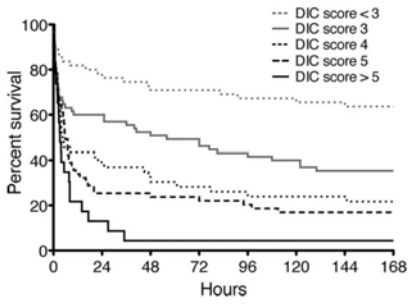
- Analyze differential survival rate during 1ST week after ROSC.
- 5 groups **(**DIC score**)**: **<3** , **3** , **4** , **5** , **>5**
- In univariable analysis, there was significant gradient of increasing hazard ratio across 5 consecutive groups (p< 0.001).
- Hazard ratio for death during the 1ST week after ROSC: (compared with first group DIC score < 3)
  Group 4 (DIC score 5): 3.95 (95% CI, 2.34–6.68)
  Group 5 (DIC score > 5) : 6.13 (95% CI, 3.30–11.38)

Table 4
Stepwise multivariateCox proportional hazard model analysis ofthe associations between early mortality risk and various potential prognostic factors.

	Hazard ratio	*p*
Age (per 1 year)	1.02 (1.01–1.03)	0.003
Shockable initial rhythm	0.49 (0.33–0.73)	<0.001
CRP (per 1 mg/dL)	1.02 (1.00–1.04)	0.047
Therapeutic hypothermia	0.38 (0.26–0.55)	<0.001
DIC scoregroups (*p*-trend < 0.001)		
1st group (DIC score 0–2, *n* = 55)	1.00 (Reference)	
2nd group (DIC score 3, *n* = 67)	1.96 (1.13–3.40)	0.017
3rd group (DIC score 4, *n* = 48)	2.26 (1.27–4.02)	0.006
4th group (DIC score 5, *n* = 59)	2.77 (1.58–4.85)	<0.001
5th group (DIC score 6–8, *n* = 23)	4.29 (2.22–8.30)	<0.001

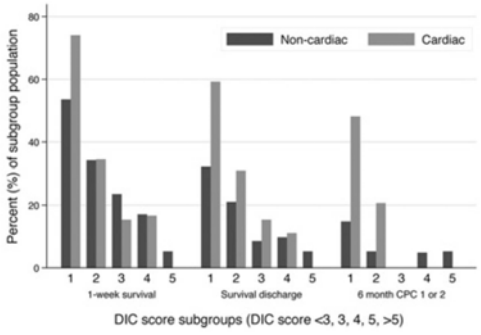
Kaplan–Meier survival curves

- The survival curves were statistically different according to the log-rank test (p = < 0.001)



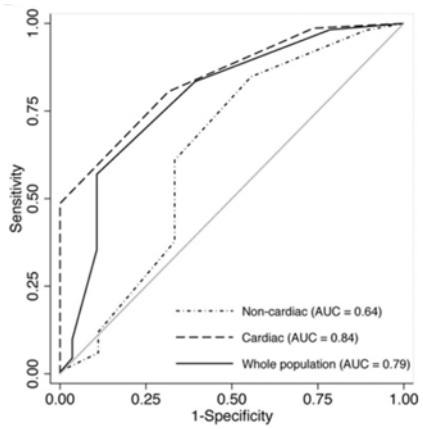
Cardiac origin vs. non-cardiac origin

- Patients with cardiac etiology: with better chance of achieving **survival discharge** (p = 0.002),**favorable long-term outcome** (p < 0.001), especially if DIC score was <5 (p = 0.006)
- **In 3rd, 4th and 5th group:** (DIC score > 3, N = 35) No one regained consciousness (CPC: 4, 5) if the cause of arrest was cardiac-origin.



Prediction of unfavorable long-term outcome

- ROC curves of DIC score; area under the curve (AUC)
- cardiac-origin subgroup: 0.84 (95% CI, 0.76–0.93)
- non-cardiac origin subgroup: 0.64 (95% CI, 0.41–0.86)
- Difference between non-cardiac and cardiac etiology subgroup was not statistically significant (p = 0.095)



Prediction of unfavorable long-term outcome

- The optimal cutoff point of DIC score for prediction of unfavorable long-term outcome:
  between DIC score 3 and 4
  (cardiac-subgroup =whole study population)
- By using the cutoff point:

sensitivity	specificity	PPV	NPV
48.6%	100.0%	100.0%	33.9%
95% CI, 36.7–60.7	95% CI, 82.2–100.0	95%CI, 89.9–100.0	95% CI, 21.8–47.8

Discussion

- The increased initial DIC score was an independent risk factor for inhospital death and unfavorable long-term outcome.
- The relationships remained significant in cardiac-cause subgroup where the influence from underlying conditions causing coagulopathy is minimized.
- High possibility that patients with higher DIC score :
  With underlying or precipitating conditions that could had already caused varying degree of coagulopathy before cardiac arrest.

Discussion

- However, the global coagulation activation of cardiac arrest per se could have significant prognostic implication.
- Previous studies: consumptive coagulopathy plays central role in pathogenesis of MODS in critical conditions such as sepsis or trauma.
- Similar global activation of coagulation pathway is also observed in cardiac arrest patients
- **In this study, significant correlation between DIC score and early mortality rate was found.**

- MODS including cardiac dysfunction is an important cause of death during early post-resuscitation period
- early coagulopathy might play a significant role in the development of MODS and subsequent increased mortality.
- Lack of data of progressive changes of hemodynamics and organ function to prove.

Limitations

- Retrospective study
- Below-goal variables: number of events per variables ratio lower than the desired ratio (>10)
- Authors did not perform multivariable model analysis in cardiac subgroup as its population size was too small for multivariable analysis.
- Chronological evaluation of hemodynamic indices, inflammatory markers and functional status of major organs was not possible.

(Availability of these data: to provide direct evidence of early pathological progressions: myocardial dysfunction, inflammation , MODS)

Conclusion

- Increased initial DIC score in OHCA was an independent predictor for poor outcomes and early mortality risk.
- Increased initial DIC score in cardiac arrest was an independent risk factor for both inhospital death and unfavorable long-term outcome.

Thanks for your attention!