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JOURNAL READING

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Clinical Factors in Predicting Acute Renal Failure caused by Rhabdomyolysis in the ED

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背景

- 橫紋肌溶解症的嚴重程度從無症狀的CK(creatine phosphokinase)上升至嚴重的ARF(Acute Renal Failure)、arrhythmias、hypovolemic shock、DIC等皆有可能
- ARF是橫紋肌溶解症嚴重且常發生的併發症
- 先前研究報告統計10~40%的橫紋肌溶解症併發ARF；ARF中有5~15%
- 預測或早期發現ARF是重要的治療方針

研究目的

- 了解橫紋肌溶解症病患有哪些因素與病患是否進展至ARF有關
- 找出能用來預測ARF與RRT(Renal Replacement Therapy)的risk factor
- 建立能預測ARF的Serum biomarker之臨界值

研究方法

- Retrospective analysis, single center, medical record review
- 收集2006-2011年，65歲以下於急診診斷橫紋肌溶解症且72小時內Serum CK上升至1000 U/L以上之病患

研究方法

- 排除以下病患
  - 有Muscular dystrophy或其他肌肉代謝問題之病患
  - 有Myocardial infarction病史之病患
  - 有CKD病史之病患
  - 入院後因其他疾病併發或醫源性所造成的橫紋肌溶解症
  - 大於65歲之病患

研究方法

- ARF(Acute Renal Failure)之定義
  - 小於19歲：Creatinine比同年齡性別97.5th percentile高
  - 大於19歲：
    - Creatinine大於4.0mg/dl
    - Creatinine每日上升超過0.5mg/dl
    - Creatinine超過病患本身baseline3倍
    - 尿量少於0.3ml/kg/hr
    - 12小時無尿
- RRT(Renal Replacement Therapy)之定義
  - 有使用PD、HD或continuous RRT

結果

- 六年共收錄202名病患，平均年齡33.4±16.3歲
- 最常見症狀為肌肉疼痛(56.7%)及肌肉無力(59.9%)
- 29名(14.4%)病患併發ARF
- 5名(2.5%)病患有用RRT治療

Table 1
Demographics and clinical presentations of the patients with rhabdomyolysis

	ARF				P
	No (n = 173)		Yes (n = 29)		
	n	%	n	%	
Age					
<19	34	19.7	3	10.3	.304
19-65	139	80.3	26	89.7	
Sex					
Female	31	17.9	3	10.3	.426
Male	142	82.1	26	89.7	
Muscle pain					
Yes	101	58.7	13	44.8	.162
No	71	41.3	16	55.2	
Muscle weakness					
Yes	99	57.2	22	75.9	.058
No	74	42.8	7	24.1	
Muscle swelling					
Yes	44	25.4	5	17.2	.341
No	129	74.6	24	82.8	
Dark urine					
Yes	26	15.0	12	41.4	.001*
No	147	85.0	17	58.6	
Fever					
Yes	46	26.6	12	41.4	.103
No	127	73.4	17	58.6	
Admission unit					
OU	45	26.2	1	3.4	<.001*
Ward	114	66.3	17	58.6	
ICU	13	7.6	11	37.9	

OU, observation unit; ICU, intensive care unit.
* Statistically significant by the χ^2 test or Fisher's exact test, when appropriate.

Table 2
Etiologies of patients with rhabdomyolysis and ARF

Cause	Total (n = 202)		ARF				P	RRT				P
			No (n = 173)		Yes (n = 29)			No (n = 24)		Yes (n = 5)		
	n	%	n	%	n	%		n	%	n	%	
Trauma	54	26.7	50	28.9	4	13.8	.026*	3	12.5	1	20.0	.032*
Exercise	28	13.9	23	13.3	5	17.2		5	20.8	0	0.0	
Seizure	8	4.0	6	3.5	2	6.9		2	8.3	0	0.0	
Infections	37	18.3	31	17.9	6	20.7		6	25.0	0	0.0	
Drugs and toxins	25	12.4	22	12.7	3	10.3		1	4.2	2	40.0	
Metabolic and electrolyte disorders	20	9.9	18	10.4	2	6.9		2	8.3	0	0.0	
Body temperature changes	6	3.0	2	1.2	4	13.8		4	16.7	0	0.0	
Idiopathic	12	5.9	12	6.9	0	0.0		0	0.0	0	0.0	
Inflammatory myopathy	1	0.5	1	0.6	0	0.0		0	0.0	0	0.0	
Muscle hypoxia	11	5.4	8	4.6	3	10.3		1	4.2	2	40.0	

* Statistically significant by the χ^2 test or Fisher's exact test, when appropriate.

Trauma所造成的橫紋肌溶解症中
有48名(88.9%)年齡大於18歲
有47名(87%)為男性

結果

- 131名(65.8%) 病患CK<5000U/L
  - 12名(9%)併發ARF
  - 1名經RRT治療
- 19名(9.4%)病患5000U/L<CK<10000U/L
  - 6名(31.6%)併發ARF
  - 無病患經RRT治療
- 50名(24.8%)病患CK>10000U/L
  - 11名(22%)併發ARF
  - 4名(8%)經RRT治療

Table 3
Comparison of laboratory tests of patients between ARF and non-ARF groups

	Non-ARF			ARF			P
	n	Mean	SD	n	Mean	SD	
WBC (×10³/L)	164	10 718.3	5146.0	29	17 138.3	7901.4	<.001*
BUN (mg/dL)	86	13.2	7.5	24	50.1	32.6	<.001*
Cr (mg/dL)	168	0.8	0.3	29	4.0	2.1	<.001*
ALT (U/L)	139	114.6	349.8	27	204.3	315.7	.218
AST (U/L)	44	321.8	603.1	18	471.4	581.4	.374
Sodium (mmol/L)	166	138.3	4.3	28	136.8	6.1	.320
Potassium (mmol/L)	164	3.6	0.7	29	4.2	1.1	.008*
CK peak (U/L)	173	10 685.4	26 062.0	29	19 698.3	32 956.7	.106
CK initial (U/L)	128	7686.1	17 475.2	19	15 575.7	30 627.5	.286
CK day 2 (U/L)	96	10 576.2	29 824.6	13	13 102.2	18 122.3	.767
CK day 3 (U/L)	66	13 881.9	35 140.8	18	22 245.7	31 189.7	.363
CK day 4 (U/L)	56	9437.3	18 516.8	12	11 637.8	11 133.1	.694
CK day 5 (U/L)	48	7783.7	14 472.3	15	11 724.7	10 940.8	.336
Myoglobin peak (ng/mL)	120	1407.1	1650.0	21	2551.3	1415.9	.003*
Myoglobin initial (ng/mL)	87	1306.2	1467.1	15	2236.9	1414.8	.025*
Myoglobin day 2 (ng/mL)	53	1176.2	1483.9	4	434.1	349.8	.014*
Myoglobin day 3 (ng/mL)	32	1189.2	1587.3	5	2458.5	2111.3	.120
Myoglobin day 4 (ng/mL)	31	831.2	1850.0	6	2184.1	1658.6	.105

ALT, alanine aminotransferase; AST, aspartate aminotransferase. ARF, acute renal failure; WBC, white blood count; BUN, blood urea nitrogen; CK, creatine phosphokinase.
* Statistically significant by Student's *t*-test.

Table 4
Multivariate logistic regression analysis of predictive factors associated with ARF caused by rhabdomyolysis

	Total (n = 202)	ARF, n (%) or mean ± SD	Odds ratio	95% CI	P
Dark urine					
No	164	17 (10.4)	1.000		
Yes	38	12 (31.6)	9.943	2.266-43.620	.002
Metabolic acidosis, n (%)					
No	193	23 (11.9)	1.000		
Yes	9	6 (66.7)	2.699	0.266-27.421	.401
Body temperature change, n (%)					
No	196	25 (12.8)	1.000		
Yes	6	4 (66.7)	366.371	18.549-7236.454	<.001
Potassium, mean ± SD	3.7 ± 0.8	4.2 ± 1.1	3.077	1.246-7.598	.015
Peak CK	11 979.3 ± 27 742.4	19 698.3 ± 32 956.7	1.000	1.000-1.000	.908
Peak myoglobin	1577.5 ± 1663.7	2551.3 ± 1415.9	1.000	1.000-1.000	.682

CI, confidence interval; WBC, white blood count; CK, creatine phosphokinase.

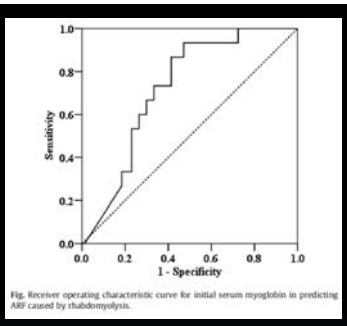


Fig. Receiver operating characteristic curve for initial serum myoglobin in predicting ARF caused by rhabdomyolysis.

- ROC分析：
  - Initial serum myoglobin的AUC為0.72 (acceptable discrimination)
  - 最佳臨界值為597.5ng/ml

結果

併發ARF的病患中...

	需要RRT治療	不需要RRT治療	
Peak BUN	72.6±28.3	44.1±31.6	p=0.043
Peak Cr	5.7±1.7	3.6±2	p=0.023
3rd 天CK	56827.5±47216.8	12365.1±16868	p=0.022

討論

- 橫紋肌溶解症的原因：
  - 小於19歲：Infection 59.5%、Trauma 16.2%、Exercise 16.2%、Metabolic & Electrolyte disturbances 5.4%
  - 大於19歲：Trauma 29.1%、Drug & Toxins 15.2%、Exercise 13.3%、 Metabolic & Electrolyte disturbances 10.9%

討論

- 早期治療並避免進展至ARF很重要，因此希望能預測哪些病人可能會發生ARF
- 先前研究曾指出Serum CK較Myoglobin能評估橫紋肌溶解的嚴重程度，可能因為CK的半衰期(1~2天)較Myoglobin(2~3小時)長
- 在這研究中initial或peak CK並沒有辦法有效預測會發生ARF之病患，唯有第三天的CK與需要RRT治療有統計上的意義

討論

- 近期有日本研究指出Peak Serum Myoglobin是能預測發生ARF的因子，臨界值為3865 ng/ml
- 有其他研究關於Myoglobin與ARF發生機率之相關，但結果不一致
- 此研究發現Initial與Peak Serum Myoglobin能預測ARF的發生，臨界值為597.5ng/ml

討論

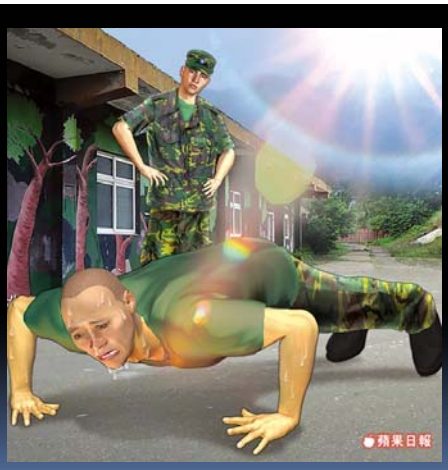
- 深茶色尿液與體溫改變所造成的橫紋肌溶解較容易進展成ARF
- 血液中的BUN, Cr, K^+也是預測ARF的重要因子
- 本研究中需要RRT的病患佔ARF中的17.2%，其中血液中的Peak BUN, Cr及第三天的CK與需要RRT治療有關

限制

- Retrospctive, single center, 病歷回顧
- 皆為65歲以下病患
- 沒有納入病患接受治療的時間與種類
- 有些病人沒有有追蹤血液中的biomarker，因此沒有peak的資料

結論

- 深茶色尿、造成橫紋肌溶解的原因、血液中BUN、Cr、initial與peak Myoglobin值與ARF之發生有相關
- 血液中Peak BUN, Cr與第三天的CK值與需要RRT有相關
- 當Initial的Myoglobin大於600ng/ml時需特別注意病患進展成ARF之可能性



Rapid Emergency Medicine Score as a main predictor of mortality in Vibrio vulnificus–related patients

Sheng-Hung Kuo MD, Chin-Feng Tsai MD, PhD, Chi-Rong Li PhD, Shih-Jei Tsai MD, PhD, Wai-Nang Chao MD, Khee-Siang Chan MD, PhD, Yuan-Ti Lee MD, PhD, Ruey-Hong Wong PhD, Chun-Chieh Chen MD, PhD, Shiuan-Chih Chen MD, PhD

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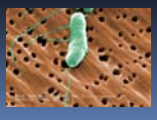


背景

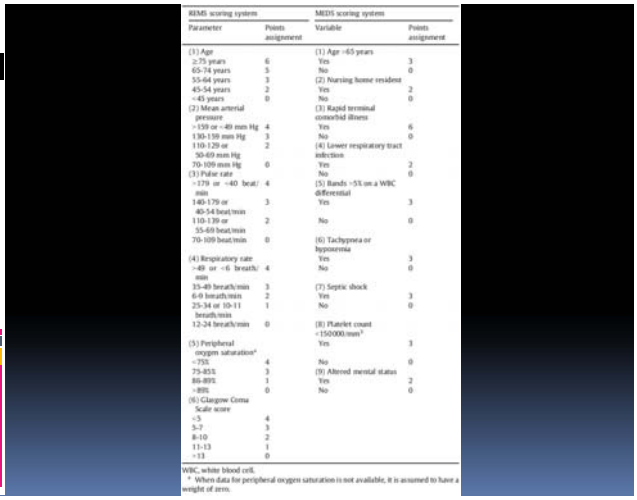
- Vibrio vulnificus為一劇毒、葛蘭氏陰性、嗜鹽、桿狀、生存於熱帶海域，每年大約有0.2~36每百萬人感染
- 進入宿主後，進展極快，並進入inflammatory、bullous、ganrenous stage
- 先前報告統計死亡率在10%~54%
- 快速辨認並有效治療很重要

研究目的

- 近期許多研究利用APACHE II score來預測死亡率，但APACHE II原是為ICU病患設計，且需要較多的實驗室數據
- REMS(Rapid Emergency Medical Score)與MEDS(Mortality in Emergency Department Sepsis)是兩個在入院時就能評估的量表
- 此研究目的為評估REMS與MEDS在預測Vibrio vulnificus死亡率之可行性

研究方法

- Retrospective analysis, single center
- 收集1999-2010年，18歲以上，由急診住院，經血液或傷口培養診斷為海洋弧菌感染之病患
- 回顧性為病患評REMS與MEDS



REMS scoring system

Parameter	Points assignment
(1) Age	
≥75 years	6
65-74 years	5
55-64 years	3
45-54 years	2
<45 years	0
(2) Mean arterial pressure	
>159 or <40 mm Hg	4
130-159 mm Hg	3
110-129 or 50-69 mm Hg	2
70-109 mm Hg	0
(3) Pulse rate	
>179 or <40 beat/min	4
140-179 or 40-54 beat/min	3
110-139 or 55-69 beat/min	2
70-109 beat/min	0
(4) Respiratory rate	
>49 or <6 breath/min	4
35-49 breath/min	3
6-9 breath/min	2
25-34 or 10-11 breath/min	1
12-24 breath/min	0
(5) Peripheral oxygen saturation[a]	
<75%	4
75-85%	3
86-89%	1
>89%	0
(6) Glasgow Coma Scale score	
<3	4
3-5	3
6-10	2
11-13	1
>13	0

MEDS scoring system

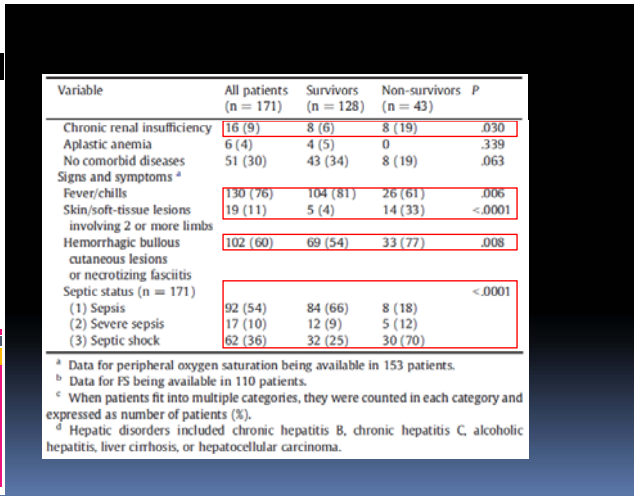
Variable	Points assignment
(1) Age >65 years	
Yes	3
No	0
(2) Nursing home resident	
Yes	2
No	0
(3) Rapid terminal comorbid illness	
Yes	6
No	0
(4) Lower respiratory tract infection	
Yes	2
No	0
(5) Bands >5% on a WBC differential	
Yes	3
No	0
(6) Tachypnea or hypoxemia	
Yes	3
No	0
(7) Septic shock	
Yes	3
No	0
(8) Platelet count <150000/mm³	
Yes	3
No	0
(9) Altered mental status	
Yes	2
No	0

WBC, white blood cell.
[a] When data for peripheral oxygen saturation is not available, it is assumed to have a weight of zero.

結果

Table 1
Demographic data, underlying diseases, and clinical features in 171 *V vulnificus*–infected patients

Variable	All patients (n = 171)	Survivors (n = 128)	Non-survivors (n = 43)	P
Age (years)	63.1 ± 12.3	62.3 ± 11.6	65.5 ± 13.9	.143
Gender, male, No. (%)	95 (56)	72 (56)	23 (53)	.755
REMS, mean ± SD (points)	6.5 ± 3.0[a]	5.4 ± 2.3[b]	9.7 ± 2.6	<.0001
MEDS, mean ± SD (points)	5.3 ± 3.9	4.2 ± 3.4	8.6 ± 3.5	<.0001
Duration of symptoms before admission (days)	1.4 ± 0.8	1.4 ± 0.8	1.2 ± 0.6	.135
Type of infection, No. (%)				<.0001
Primary septicemia	73 (43)	43 (34)	30 (70)	
Wound infection	98 (57)	85 (64)	13 (30)	
Coexisting medical conditions[c]				
Liver disease[d]	50 (29)	26 (20)	24 (56)	<.0001
Diabetes mellitus	52 (30)	36 (28)	16 (37)	.263
Malignancy	24 (14)	18 (14)	6 (14)	.986
Immunosuppressive agent/steroid used	39 (23)	33 (26)	6 (14)	.110



Variable	All patients (n = 171)	Survivors (n = 128)	Non-survivors (n = 43)	P
Chronic renal insufficiency	16 (9)	8 (6)	8 (19)	.030
Aplastic anemia	6 (4)	4 (5)	0	.339
No comorbid diseases	51 (30)	43 (34)	8 (19)	.063
Signs and symptoms[a]				
Fever/chills	130 (76)	104 (81)	26 (61)	.006
Skin/soft-tissue lesions involving 2 or more limbs	19 (11)	5 (4)	14 (33)	<.0001
Hemorrhagic bullous cutaneous lesions or necrotizing fasciitis	102 (60)	69 (54)	33 (77)	.008
Septic status (n = 171)				<.0001
(1) Sepsis	92 (54)	84 (66)	8 (18)	
(2) Severe sepsis	17 (10)	12 (9)	5 (12)	
(3) Septic shock	62 (36)	32 (25)	30 (70)	

[a] Data for peripheral oxygen saturation being available in 153 patients.
[b] Data for FS being available in 110 patients.
[c] When patients fit into multiple categories, they were counted in each category and expressed as number of patients (%).
[d] Hepatic disorders included chronic hepatitis B, chronic hepatitis C, alcoholic hepatitis, liver cirrhosis, or hepatocellular carcinoma.

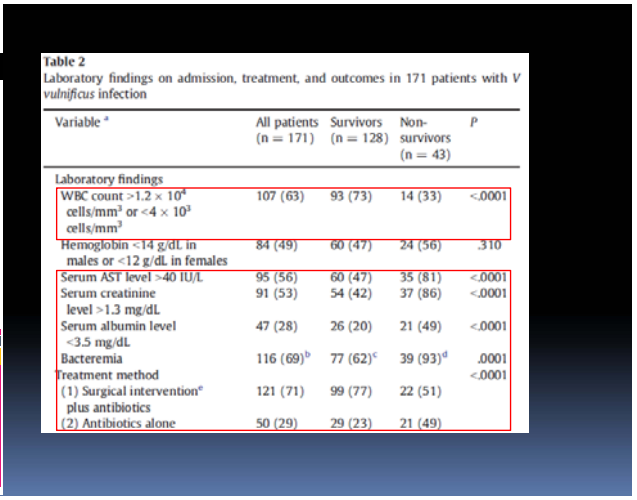
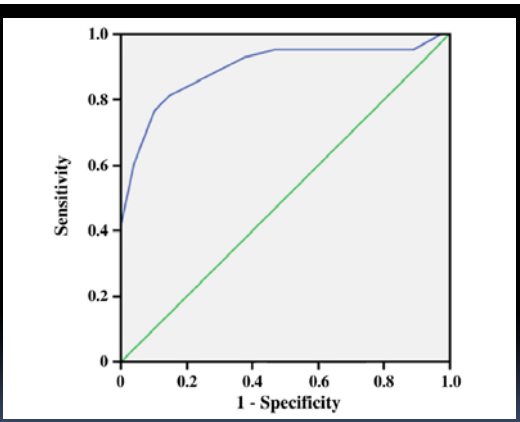


Table 2
Laboratory findings on admission, treatment, and outcomes in 171 patients with *V vulnificus* infection

Variable[a]	All patients (n = 171)	Survivors (n = 128)	Non-survivors (n = 43)	P
Laboratory findings				
WBC count >1.2 × 10⁴ cells/mm³ or <4 × 10³ cells/mm³	107 (63)	93 (73)	14 (33)	<.0001
Hemoglobin <14 g/dL in males or <12 g/dL in females	84 (49)	60 (47)	24 (56)	.310
Serum AST level >40 IU/L	95 (56)	60 (47)	35 (81)	<.0001
Serum creatinine level >1.3 mg/dL	91 (53)	54 (42)	37 (86)	<.0001
Serum albumin level <3.5 mg/dL	47 (28)	26 (20)	21 (49)	<.0001
Bacteremia	116 (69)[b]	77 (62)[c]	39 (93)[d]	.0001
Treatment method				<.0001
(1) Surgical intervention[e] plus antibiotics	121 (71)	99 (77)	22 (51)	
(2) Antibiotics alone	50 (29)	29 (23)	21 (49)	

Variable [a]	All patients (n = 171)	Survivors (n = 128)	Non-survivors (n = 43)	P
Antibiotic treatment				.201
(1) Penicillin group or first-/second-generation cephalosporin with or without an aminoglycoside	31 (18)	26 (20)	5 (12)	
(2) Third-generation cephalosporin with minocycline (or analogue) or quinolone group	140 (82)	102 (80)	38 (88)	
Mechanical ventilatory support needed	14 (8)	6 (5)	8 (19)	.008
Hemodialysis/hemofiltration needed	5 (3)	1 (1)	4 (9)	.015
Vasopressor administration	62 (36)	32 (25)	30 (70)	<.0001
Time to surgical treatment after admission < 24 hours	105 (87)[f]	93 (94)[g]	12 (55)[h]	<.0001
Limb amputation needed	9 (5)	9 (7)	0	.114
ICU admission needed	68 (40)	39 (31)	29 (67)	<.0001
Hospital stay, mean ± SD (days)	16.8 ± 14.6	20.9 ± 16.6	4.6 ± 4.5	<.0001



REMS之AUC=0.895 (excellent discrimination)
(95%CI=0.840-0.937; p<0.0001)

REMS≥8較REMS<8有高死亡率
(adjusted OR, 26.6; 95% CI, 15.5-79.9; p<0.0001)
REMS≥8較REMS<8高入ICU率(72% vs 25%)
(adjusted OR, 12.5; 95% CI, 5.2-30.2; p<0.0001)

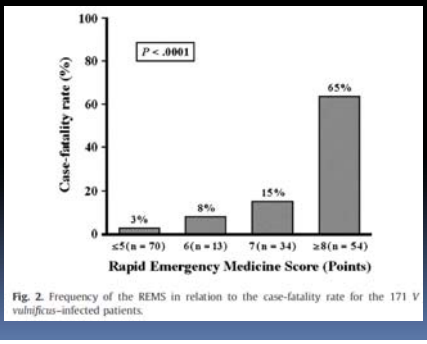


Fig. 2. Frequency of the REMS in relation to the case-fatality rate for the 171 *V vulnificus*–infected patients.

討論

- 較高REMS、肝病、Hemorrhagic bullous/necrotizing fascitis與死亡率有關
- 住院24小時內手術有減少死亡率
- REMS≥8時死亡率上升(adjusted OR 26.6)
- REMS≥8時入ICU率上升(adjusted OR 12.5)

討論

- 先前研究使用APACHE II來預測海洋弧菌感染之死亡率，但有其限制
- REMS預測死亡率之AUC為0.895，sensitivity與specificity皆大於80%
- 能有效早期辨別死亡率較高之病患、評做病患疾病嚴重程度

限制

- 海洋弧菌感染不常見，使大規模前瞻性研究較難
- 並非所有病患之資料皆完整(其中周邊血氧之完整度較差)
- 單一機構，回顧性研究

結論

- REMS是個快速能評估受海洋弧菌感染病患之嚴重程度的工具，辨別能力高
- 肝病、Hemorrhagic bullous/necrotizing fascitis與死亡率有關
- 住院24小時內手術能減少死亡率