The predictive value of admission and follow up factor V and VII levels in patients with acute hepatitis and coagulopathy

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Background/Aims: Low factor V and VII levels are bad prognostic indicators in fulminant hepatic failure (FHF). The prognostic importance of admission versus follow up levels of these factors in patients with acute hepatitis and coagulopathy without encephalopathy has not been evaluated.

Methods: Clinical and laboratory data from 68 consecutive patients with acute hepatitis and coagulopathy but without encephalopathy, during a 6-year period, was retrospectively evaluated.

Results: Sixty patients (88%) demonstrated improvement in liver function and coagulation ('survivors'), while 8 patients (12%) died or underwent OLT ('non-survivors'). Survivors had higher admission ($P<0.005$) and follow up factor VII levels ($P<0.005$) than non-survivors. Follow up factor V levels were higher in survivors ($P<0.02$), while admission factor V level was not different between groups ($P=$ NS). Multivariate logistic regression analysis demonstrated that admission factor VII levels predicted outcome ($P<0.006$). Area under the ROC curve of factor VII was larger than that of factor V (0.885 and 0.715, respectively, $P<0.02$). After 3 days of hospitalization, factor V levels, but not factor VII, independently predicted outcome ($P<0.04$).

Conclusions: In patients with hepatitis and coagulopathy without encephalopathy at presentation, admission factor VII level may serve as a reliable prognostic marker. Subsequently, during hospitalization, changes in factor V are better outcome indicators.

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1. Introduction

Acute hepatic failure is often associated with a wide spectrum of coagulation abnormalities, mainly due to reduced hepatic production and increased peripheral consumption of coagulation factors [1]. Prolongation of prothrombin time is associated with poor outcome in patients with acute liver failure [2]. Due to their relatively short half-lives, factors V and VII are commonly used in prognostic evaluation in this setting [3–6].

Many patients, presenting with acute hepatitis that is associated with coagulopathy, do not fulfill other criteria for acute liver failure at presentation. Many of these patients develop prolonged prothrombin time and reduced levels of factor V and VII, but fully recuperate and regain normal hepatic synthetic function shortly afterwards. Only a minority of these patients feature worsening hepatic function and develop life-threatening fulminant hepatic failure. Early identification of this small subgroup of patients is crucial, since early referral to liver transplantation centers is needed.

The associations between admission and follow up levels of factors V and VII in patients without fulminant hepatic

failure has not been widely reported [7]. In our study, 68 consecutive cases of patients with hepatitis and coagulopathy were retrospectively evaluated, and the correlation between factor V and VII levels at admission and during follow up hospitalization and the subsequent outcome were assessed.

2. Methods

2.1. Patients

We reviewed the records of all patients who were admitted to Hadassah-Hebrew University Medical centers, Jerusalem, Israel between the years 1998 and 2003. The participating hospitals serve as primary, secondary and tertiary medical care facilities and perform liver transplantation. Included were patients who presented with liver enzyme elevation compatible with acute liver injury that was associated with a significant new-onset prolongation of prothrombin time (PT), defined as an INR level of greater than 1.7. Excluded were patients that fulfilled criteria for acute liver failure at presentation (including encephalopathy of any grade, hepatorenal syndrome, or multiorgan failure), those patients were divided into two groups according to outcome, to those who featured resolution of acute liver injury with normalization of coagulation abnormalities ('survivors'), and those who either died or required urgent orthotopic liver transplantation ('non-survivors').

2.2. Clinical and mortality information

Information was recorded using the patients' medical charts, including patient clinical records. Data included age, sex and etiology of acute hepatitis. Information on mortality was obtained using patients' medical records, liver unit transplantation records, and death certificates.

2.3. Laboratory evaluation

Aminotransferase activity and bilirubin, creatinine, urea, albumin and prothrombin time (PT) were recorded using standard automated procedures (automated chemistry analyzer Kodak-Vitros 950, Rochester, NY, USA and the coagulation time analyzers Acl 200 and 1000). Levels were monitored daily from admission until resolution of hepatitis, death, or transplantation.

Factors V and VII were measured at presentation in all patients using the same plasma sample. Factor measurements were performed according to international guidelines [8]. Patients' plasma was added to factor-deficient plasma. Coagulation time was compared to that of control plasma mixed with factor deficient plasma. Results were expressed as percents of control. Factor V and VII levels were measured repeatedly throughout the hospitalization period as clinically indicated. All laboratory tests were made by the same laboratory, using the same kits.

2.4. Data analysis

Fisher exact test and ANOVA method were used for the detection of differences in age, sex and etiology of hepatitis between the survivor and non-survivor groups. Fisher exact test, Mann–Whitney test and ANOVA were used to evaluate other differences in clinical and laboratory parameters. Continuous variables are presented as mean$\pm$SD. All statistical tests were two-tailed, and a *P*-value lesser than 0.05 was considered significant. Prediction of outcome was assessed by multivariate logistic regression, including admission parameters that were found to be significantly associated with outcome in univariate analyses. Statistical analyses and ROC curves were generated by Analyse-it software for Microsoft Excel.

3. Results

3.1. Baseline characteristics of the study population

Sixty-eight patients were admitted with hepatitis that was associated with coagulation abnormalities at presentation. The duration between onset of disease and admission ranged between 1 and 7 days. The survivor group included 60 patients (88%) who featured complete resolution of acute hepatitis, all within 3 weeks of admission (range 10–21 days). The non-survivor group included 5 patients (7%) who underwent successful liver transplantation, and 3 patients (4%) who died of FHF complications (e.g. brain edema, multiorgan failure, and sepsis). Baseline characteristics of the two study groups are shown in Table 1. The demographic parameters were not significantly different between survivors and non-survivors.

3.2. Clinical and laboratory presentation

Etiology of hepatitis differed between survivors and non-survivors (Table 1); there was a higher proportion of subjects with a favorable etiology (i.e. acetaminophen overdose, hepatitis A and hepatitis B) in the survivor group (58% versus 13% in non-survivors, $P<0.04$). All 12 patients with acetaminophen overdose survived. Laboratory values at presentation are listed in Table 1. Serum creatinine, urea, albumin, aspartate aminotransferase activity (AST) and alanine aminotransferase activity (ALT) did not differ significantly between patient groups. In contrast, total bilirubin levels were significantly higher in non-survivors $(335\pm203~\mu mol/l)$ than among survivors $(118\pm132~\mu mol/l, P<0.0001)$.

Table 1
Demographic clinical and laboratory data of the study groups

	Survivors ($n=60$)	Non-survivors ($n=8$)	*P* value
Age (years)	32 ± 19	21 ± 13	NS
Female gender (%)	34 (57)	2 (25)	NS
Etiology of hepatitis (%)			
Paracetamol	10 (17)	0 (0)	NS
Other drug/toxin	6 (10)	0 (0)	NS
Autoimmune	7 (12)	2 (25)	NS
Hepatitis A	17 (28)	1 (12.5)	NS
Hepatitis B	8 (13)	0 (0)	NS
Non-A, non-B	2 (3)	2 (25)	NS
Miscellaneous	5 (8)	1 (12.5)	NS
Unknown	5 (8)	2 (25)	NS
Bilirubin (µmol/l)	118 ± 132	335 ± 203	0.0001
Creatinine (µmol/l)	99 ± 207	85 ± 79	NS
Urea (mmol/l)	4.6 ± 5.3	3.8 ± 4.2	NS
Albumin (g/dl)	3.5 ± 0.6	3.2 ± 0.5	NS
AST (u/l)	2564 ± 4279	2385 ± 3755	NS
ALT (u/l)	2428 ± 2782	1604 ± 1543	NS

Table 2
Admission and follow up coagulation factor levels

		Survivors ($n=68$)	Non-survivors ($n=10$)	P value
Factor V, %	Admission	79 ± 44	51 ± 23	0.08
	Nadir level	74 ± 41	39 ± 11	<0.02
Factor VII, %	Admission	34 ± 19	13 ± 5	<0.005
	Nadir level	30 ± 16	11 ± 5	<0.005

3.3. International normalized ration (INR), factor V and VII levels at presentation and during hospitalization

INR was not statistically different between survivors (4.1 ± 3.9) and non-survivors (6.5 ± 3.5, $P=0.07$). In a univariate logistic regression analysis INR did not predict outcome, $P>0.08$. Admission plasma factor V and factor VII levels are demonstrated in Table 2. Factor VII levels were significantly lower in non-survivors than in survivors (13 ± 5 versus $34\pm19\%$ for survivors, $P<0.005$). In contrast, factor V levels were not significantly different between non-survivors ($51\pm23\%$) and survivors ($79\pm44\%$, $P=$NS). During follow up hospitalization, the lowest nadir measured levels of both factor V and factor VII in non-survivors ($39\pm11\%$ and $11\pm5\%$, respectively) were significantly lower than in survivors ($74\pm41\%$ and $30\pm16\%$ for factor V and VII in survivors, $P<0.02$ and $P<0.005$, respectively).

3.4. Association between admission factor V and VII levels and non-survival

Sensitivity–specificity analyses for the prediction of non-survival by admission values of bilirubin, factors V and VII are depicted in Table 3. Receiver operator characteristic (ROC) curves analyzing the accuracy of factors V and VII in predicting non-survival are plotted in Fig. 1. The area under the ROC curves is 0.715 (95% CI 0.592–0.818) for factor V and 0.885 (95% CI 0.785–0.953) for factor VII. The difference between the curves is statistically significant ($P<0.02$). The area under the ROC curve of bilirubin (not shown) was 0.835 (95% CI 0.726–0.914), which was insignificantly different from that of factors VII and V.

Univariate and multivariate logistic regression analyses of the association between outcome and admission parameters that differed between subgroups, namely etiology of liver disease, bilirubin, and factor VII, found that etiology did not predict outcome ($P=$NS), while high total bilirubin

Table 3
Accuracy of admission levels of bilirubin, factor V and factor VII in the prediction of non-survival

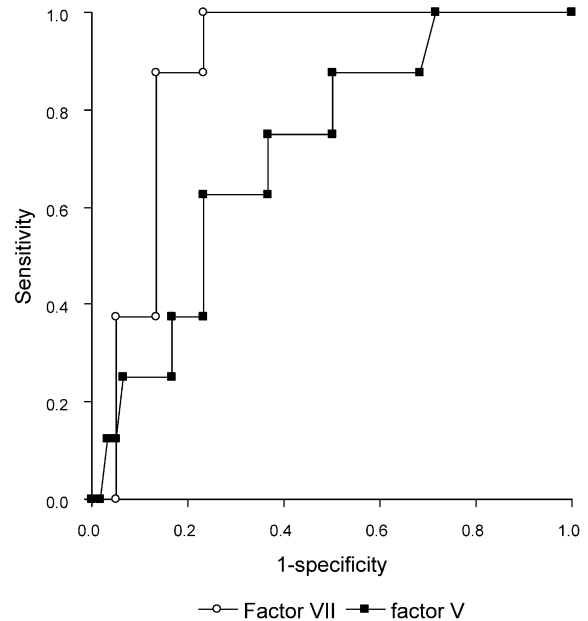| Parameter	Cut-off value	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Bilirubin	250 μmol/l	75 (35–96)	87 (75–94)
Factor V	47%	63 (25–91)	77 (64–87)
Factor VII	20%	100 (63–100)	77 (64–87)

Fig. 1. Receiver operating characteristic curves analyzing the accuracy of predicting non-survival by admission factor V levels (closed rectangles) and factor VII levels (open circles). The difference between the areas under the curves is significant, $P<0.02$.

and low factor VII both significantly predict non-survival ($P<0.005$ and $P<0.006$, respectively).

3.5. Association between follow up factor V and VII levels and non-survival

On the second hospitalization day, clinical improvement and restitution of INR and of factor levels were observed in 22 patients (32%). All these patients survived. Repeated re-evaluations of factor levels during hospitalization were performed in the rest of the 46 patients (68%). When third day factor levels were compared to admission levels, a reduction in factor V level, but not factor VII level, predicted impending deterioration.

Among a subgroup of 22 patients who, at presentation, featured factor VII levels lower than 21%, a drop in factor V levels from day 1 to 3 of hospitalization was associated with an odds ratio for non-survival of 1.13 ($P=0.07$) for every 1% decrease in factor level. The area under the ROC curve for the prediction of outcome adapted to the change in factor V during the first three hospitalization days (Fig. 2) is 0.827 (95% CI 0.586–0.957), while the corresponding value for the change in factor VII is insignificant (not shown). An increase of 2% or more in factor V levels had 100% negative predictive value for non-survival.

3.6. Analysis that included patients with encephalopathy at presentation

To avoid selection bias by the exclusion of patients with a more severe disease, we also evaluated factor V and VII
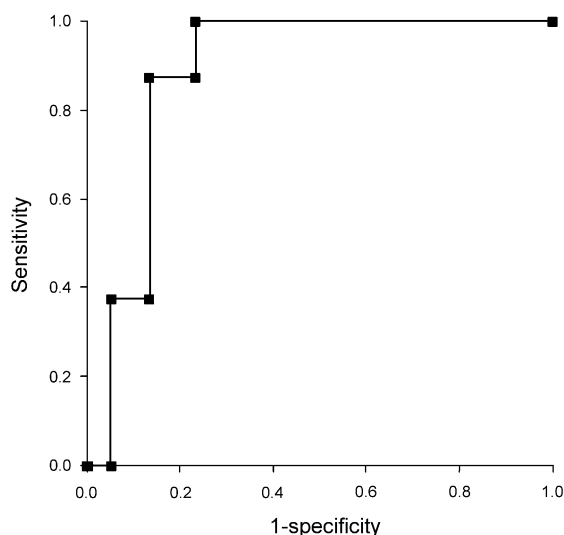
Fig. 2. Receiver operating characteristic curve analyzing the accuracy of predicting non-survival by the drop in factor V levels during the first three days of hospitalization.

predictive power for mortality in all patients that presented at our medical center with acute hepatic damage and coagulation abnormalities during the study period. This summed up to a total of 78 patients—the above 68 patients in addition to 10 patients who featured evidence of liver failure at presentation. Even in this larger group, admission factor VII levels were significantly lower among non-survivors ($15\pm7\%$) than among survivors ($32\pm19\%$, $P<0.001$). Admission factor V levels did not differ significantly between non-survivors ($51\pm21\%$) and survivors ($76\pm43\%$, $P=$NS).

Fifty four of the 78 patients (69%) had their factors re-measured 3 days after admission, including 8 of the 10 patients with acute liver failure at presentation (the 2 remaining patients either died or were transplanted within 24 h of presentation). Thirty-six of them featured low factor VII levels at presentation of less than 21% (26 survivors, 10 non-survivors). The area under the ROC curve of the change in factor V is 0.836, while the corresponding value for the change in factor VII is 0.604 ($P<0.04$ for the difference between the ROC curves).

4. Discussion

This retrospective study demonstrates that in patients who present with acute liver injury that is associated with coagulation abnormalities but without encephalopathy, admission factor VII levels, but not factor V, was of significant prognostic importance. We demonstrated that all patients who have eventually died or required liver transplantation had admission factor VII levels that were 20% or less of control. On the other hand, improving factor V levels during the first 3 days of hospitalization were reliably predictive for an improved outcome, while worsening factor V levels predicted impending deterioration.

Practicing physicians are often faced with dilemmas in regard to the management of patients who suffer of acute liver injury in association with coagulation abnormalities. First they need to recognize these patients that are at risk of progression to acute liver failure, and require careful in-hospital monitoring, preferentially at liver specialized intensive care units. Second, they need to decide on the best timing for liver transplantation in patients who continue to deteriorate after admission. A prognostic test that is highly sensitive, that does not fail to detect any patient with a potential for deterioration, and that does not rely on the etiology of liver injury, which is commonly unknown at presentation, is needed.

Most previously published studies included patients with fulminant hepatic failure at presentation. The application of the results from these studies to patients with less severe forms of acute liver injury may create a bias, as most bad prognostic signs are not recognizable in such patients. Our study, on the other hand, included only patients with acute liver injury and coagulopathy but without encephalopathy, so it avoids such bias and thus closely reflects the clinical setting during patient evaluation. In primary care facilities, we suggest that admission factor VII levels of more than 20% are indicators of subsequent improvement. No such association is demonstrable for admission INR or factor V levels. Nevertheless, even when patients with fulminant hepatic failure at presentation were included, admission factor VII levels remained a statistically significant prognostic indicator.

As for the second dilemma, concerning the decision-making process in regard to timing of patient referral for liver transplantation, several parameters have been previously suggested, including etiology (Wilson's disease, idiosyncratic drug reactions, and Budd-Chiari syndrome conferring a bad prognosis), age, duration of jaundice, level of encephalopathy at presentation, creatinine, potassium and phosphate levels, white blood cell count, APACHE (acute physiology and chronic health evaluation) score, serial alpha-fetoprotein measurements, blood lactate levels, and serum levels of vitamin D binding protein. [2,8–12]. The two most widely used sets of prognostic criteria in fulminant hepatic failure, King's College and Clichy criteria, include INR and factor V levels, respectively, in prognostic assessment [2,6,13]. Bilirubin levels have been recently suggested to correlate with mortality [14]. In our study, bilirubin levels were independently correlated with mortality, even when included in a multivariate analysis together with the other tested parameters. In concert with other studies, our study demonstrated that changes in factor V levels during hospitalization are directly correlated with outcome.

One may speculate that factor VII production in acute liver injury is impaired earlier and with lesser degrees of

hepatic insult, making it a more sensitive synthetic parameter than factor V. The milder hepatic disturbance in our patient population might have enabled the recognition of the differences in sensitivity between factors. Avitaminosis K could possibly cause low factor VII levels and could overestimated liver failure, but does not explain the significant association between admission factor VII levels and survival. Nevertheless, all patients in our institution who present with disturbed INR levels in association with hepatic damage were routinely treated with vitamin K supplementation. Only two small studies, published in the early 1970s, concurrently examined admission factor V and VII levels in fulminant hepatic failure, and suggested that only factor VII level be used as an early prognostic indicator [15,16]. Later studies demonstrated that both factor V or factor VII levels are of prognostic importance in fulminant liver failure [1,3,17–22]. In contrast to our study, all these studies included patients with FHF at presentation and examined either factor V or VII, without direct comparison between them in the same patient group. None of these studies examined the importance of serial changes in factor V and VII levels during patient follow up. Thus, our study is unique in selection of patients with milder hepatic injury at presentation and with simultaneous assessment of factor V and VII.

Our study has several limitations. First, it is small and as such is subjected to selection bias. Consequently, it is too small for analysis of special subgroups, such as acetaminophen overdose that is associated with higher rates of coagulation disturbances. Larger studies should evaluate possible association in such subgroups between factor levels and mortality. Second, it is retrospective in nature, and as such its conclusions should be interpreted cautiously until prospective data validates its results. Nevertheless, despite the small size of our study, the fact that a significant correlation was found between admission factor VII level and outcome has a major clinical importance. It provides a common, easily performed tool for the recognition of patients at increased risk for adverse events at the initial point of evaluation, prior to the elucidation of the entity causing liver injury.

In conclusion, we suggest that factor VII levels be routinely measured in all patients that present with liver injury and coagulation abnormalities. Patients presenting with acute hepatitis associated with factor VII of 20% or less than control, even in the absence of other bad prognostic signs, be considered at increased risk for the development of acute liver failure and adverse outcome, and as such be aggressively monitored and treated. Larger studies should be conducted in order to prospectively validate our findings, and further evaluate the prognostic importance of factor levels at admission and several days after admission in patients with acute liver injury.

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