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Severe acute autoimmune hepatitis: How to early predict who will not respond to corticosteroids and needs urgent liver transplantation?

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ABSTRACT

Backround: In acute severe autoimmune hepatitis (AS-AIH), the early identification of predictors of non-response to corticosteroids and the optimal timing for liver transplantation (LT) remains controversial.
Aims: To determine early predictors of non-response to corticosteroids and to assess the usefulness of severity scores, namely the recently developed SURFASA.
Methods: Retrospective multicentre cohort study including consecutive patients admitted for AS-AIH between 2016 and 2020. Definitions- response to corticosteroids: LT-free survival at 90 days (D90); SURFASA score: -6.8 + 1.92x(D0-INR)+1.94xINR[(D3-D0)/D0]+1.64xbilirubin[(D3-D0)/D0].
Results: We included 26 patients [median age 56 (45–69) years; 22 (84.6%) women]. All patients underwent corticosteroid therapy. Overall survival reached 73%. amongst the non-responders, 2 (7.8%) underwent LT and 5 (19.2%) died. The interval between admission and initiation of corticosteroids was not different between responders and non- responders [13 (7–23) vs. 8 (3–10), P:0.06], respectively. SURFASA and MELD-Na^+ (D3) scores showed an AUROC of 0.96 (0.87–1) and 0.92 (0.82–0.99), respectively, for prediction of non-response. SURFASA >-2.5 had a sensitivity of 85.7% and a specificity of 100% and MELD-Na^+ (D3) >26 had sensitivity of 85.7% and a specificity of 78% for the prediction of non-response.
Conclusions: SURFASA and MELD-Na^+ at D3 scores are useful in early identification of non-responders to corticosteroids.

1. Introduction

Autoimmune hepatitis (AIH) is a rare, immune-mediated, inflammatory condition of the liver that is characterised by circulating autoantibodies, hypergammaglobulinemia and distinctive features on liver biopsy [1]. AIH has a diverse spectrum of clinical presentations, ranging from acute hepatitis to chronic hepatitis and cirrhosis. The exact proportion of patients presented with AIH is unknown but ranges from 20% to 70% in some series [2]. With an acute presentation of AIH, one might have the diagnostic dilemma of whether it represents true 'de novo' disease or a spontaneous exacerbation, superimposed infection, or drug-induced liver injury on a background of pre-existent liver disease. In the absence of pre-existing liver disease, acute severe-AIH (AS-AIH) is defined as an acute presentation of AIH characterized by jaundice and coagulopathy [international normalized ration (INR)≥ 1.5]. A proportion of these patients develop hepatic encephalopathy (HE). This condition is named AS-AIH with acute liver failure (ALF).

Managing the population with AS-AIH is a considerable challenge. The standard paradigm of management of acute AIH is corticosteroid therapy, that induces remission in 80% of the cases. The utility of corticosteroids in acute severe presentations is less well established, with an increased likelihood of treatment failure. European Association for the Study of the Liver clinical practice guidelines suggest that its optimum treatment comprises high doses of corticosteroids (≥1 mg/kg/day) and any lack of improvement within 7 days should lead to the patient being listed for emergency liver transplantation (LT) [3]. Various studies have been conducted

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to determine prognostic predictors of corticosteroid non-response, but the evidence is scarce and conflicting. Some preceding studies have shown that bilirubin and INR levels at presentation may predict corticosteroids response [4–6]. Other studies demonstrated that MELD score inferior to 27 [7] and United Kingdom Model for End-Stage Liver Disease (UKELD) score inferior to 57 at admission may correlate with treatment response [4]. Conversely, Yeoman et al. demonstrated no significant difference in MELD score at admission between corticosteroid responders and non-responders [8]. Additionally, the presence of low-grade HE and absence of massive hepatic necrosis on histology seem to be associated with corticosteroid response [5,7]. Assessing response once corticosteroids have started, deteriorating bilirubin and INR level after 3.7 days of therapy were associated with poor prognosis [9]. Miyake et al. indicate that the key time to assess the most significant difference in bilirubin level between survivors and non-survivors was from 8 to 15 days after corticosteroids initiation [5]. Another study showed that failure to improve MEL-Na^+ or UKELD scores within 7 days of corticosteroid therapy indicates a high risk of progressing to ALF [4]. A multicentre French study, evaluating patients with AS-AIH proved that the evolution of INR and bilirubin values after 3 days of therapy were highly predictive of LT or death. De Martin et al. developed a score including INR at the time of corticosteroids initiation and the variation of INR and bilirubin between the first and third day after corticosteroid initiation, named SURFASA, that may identify non-responders. However, this score needs to be validated [6].

To conclude, there is a need for early reliable prognostic predictors to facilitate patient selection for LT. If the point of corticosteroid rescue has passed and there is no improvement in bilirubin, INR or MELD-Na^+ after 7 days of therapy, continuing them may be futile and patients should be assessed for urgent LT [3]. Although this is a useful parameter in assessing response, in clinical practice, a quicker time frame for assessment would be more valuable in patients who deteriorate rapidly. Especially, for the sickest cohort, an earlier assessment, at day 3 of corticosteroid therapy, requires further evaluation.

The primary aim of this study was to determine early (third day of therapy) predictive factors for a non-response to corticosteroids, defined as a need for LT or death within 90 days of treatment initiation in patients with AS-AIH and to assess the usefulness of severity scores, namely the recently developed SURFASA.

2. Materials and methods

2.1. Study design

This was a retrospective cohort study conducted at six Portuguese Tertiary Centres, performed from January 2016 to December 2020.

2.2. Inclusion and exclusion criteria

In the absence of standardized criteria for diagnosis of AS-AIH, we adopted the definition proposed by De Martin et al. [6]: i. no previous medical history of AIH; ii: a simplified International Autoimmune Hepatitis Group (IAIHG) score that was definitive or probable; iii: an INR value $\geq$ 1.5 and/or total bilirubin$\geq$ 11.7 mg/dL at admission or at the initiation of corticosteroids. Patients without liver biopsy before steroid introduction were excluded. All consecutive patients fulfilling these criteria were included. Response to corticosteroids: LT-free survival at 90 days since initiation of the therapy. Non-response to corticosteroids: LT or death with 90 days since initiation of the therapy. The decision to initiate corticosteroid therapy, the dose, and the route of administration (oral or intravenous) were at the discretion of the Assistant Medical Doctor. Infections were identified by reports of positive tests for bacteria or viruses in the blood, urine and ascites, or from radiological signs suggestive of pulmonary infection at any time since hospital admission.

2.3. Demographic, clinical, endoscopic and histologic variables

All data were collected from medical reports. Baseline characteristics: age, gender, presence and grade of HE, presence of ascites, liver enzymes, platelet count, creatinine, sodium level, albumin, INR, Immunoglobulin G, anti-nuclear antibodies (ANA) and anti-smooth muscle antibodies (ASMA) levels and IAIHG score. The same variables were recorded at day of corticosteroid initiation (D0) and third day of therapy (D3). The MELD-Na^+ and UKELD scores were calculated at D0 and D3. The SURFASA score comprises 3 parameters: the baseline INR, the change in INR over 3 days and the change in total bilirubin over 3 days after initiation of steroids. SURFASA was calculated by the formulae $-6.8 + 1.92$x(D0-INR)+1.94xINR[(D3-D0)/D0]+1.64xbilirubin[(D3-D0)/D0] and was registered [6]. We also recorded the corticosteroid dose, route of administration, the time between admission and steroid introduction, the time between steroid introduction and LT or death and the time between the inscription on the waiting list and LT. LT-free free survival at 90 days since initiation of the therapy, as well as non-response were also collected.

2.4. Statistical analysis

Continuous variables were reported as mean and standard deviation or median and interquartile range, if they had a normal or skewed distribution, respectively; categorical variables as absolute and relative frequencies. Continuous variables were compared between two groups using *Student's T* test if they had a normal distribution and homogeneity of variance or *Mann-Whitney U* test if these conditions were not meet. Categorical variables were compared using *Pearson's* X^2 or *Fisher's exact* tests. To compare patients' responders and non-responders to corticosteroids, univariate analysis was performed using the Chi-square and Student's t tests, for categorical and continuous variables, respectively. Covariates with P value inferior to 0.05 in the univariate analysis were included in the multivariate analysis. The effect of factors on non-response were quantified using odds ratio (OR) with 95% confidence interval (CI) in both analyses. The performance of MELD-Na^+ (D3) and SURFASA in predicting response were assessed by area under the receiver operator characteristic curves (AUROC). Diagnostic accuracy of the suggested cut-off values was assessed by sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% of CI. A Pair-wise comparison of AUROC between SURFASA and MEL-Na^+ (D3) was performed. All hypotheses are two-tailed and a P-value $<$0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 25 (SPSS Inc., Chicago, Illinois, USA).

3. Results

We included 26 patients, all of them directly admitted to a tertiary centre, with a median age of 56 (45–69) years-old and 22 (84,6%) were female. At admission 3 (11.5%) had ascites and 10 (38.4%) had HE. Their median INR was 1.5 (1.3–2.2), 8 (31%) of patients had an INR inferior to 1.5. The median total bilirubin was 14.2 (10.2–19.6) mg/dL, 17 (65.4%) had a total bilirubin inferior to 11.7 mg/dL. Median creatinine was 0.78 (0.63–0.9) mg/dL. Their median MELD-Na^+ and UKELD scores at admission were 23 (20–26) and 61 (59–63), respectively. The median Immunoglobulin G value was 21 (17–30) g/L. In 19 (73%) patients, anti-nuclear

Table 1
Characteristics of the overall population with acute severe autoimmune hepatitis at hospital admission ($n = 26$).

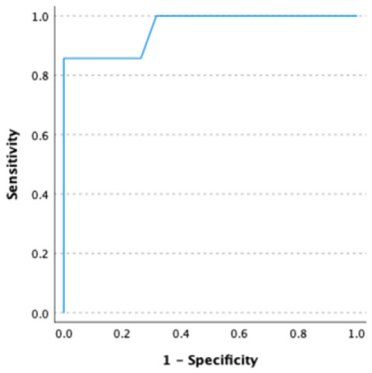
Age – median (IQR)	56 (45–69) years
Female gender – n (%)	22 (84.6)
Ascites – n (%)	3 (11.5)
Hepatic encephalopathy – n (%)	10 (38.4)
INR – median (IQR)	1.5(1.3–2.2)
Total bilirubin – median (IQR)	14.2 (10.2–19.6) mg/dL
Creatinine – median (IQR)	0.78 (0.63–0.9) mg/dL
MELD-Na$^+$ at admission – median (IQR)	23 (20–26) points
UKELD at admission – median (IQR)	61 (59–63) points
Immunoglobulin G – median (IQR)	21 (17–30) g/L
ANA and/or ASMA $\geq$ 1/80 – n(%)	19 (73)
Time until corticotherapy initiation	11 (7–18) days
Simplified IAIHG criteria	
- Definite diagnosis	11 (42.3)
- Probable diagnosis	15 (57.7)
Simplified IAIHG score – median (IQR)	6 (6–7) points
Corticosteroids dose – n(%)	
−1 mg/kg/day	23 (88.5)
−0.5 mg/kg/day	3 (11.5)
Corticosteroids response – n(%)	
- Death	2 (7.8)
- Liver Transplantation	5 (19.2)
- Response	19 (73)

antibody (ANA) and/or anti-smooth muscle antibody (ASMA) were present at titres ranging from 1:40 to 1:1280. According to the simplified IAIHG criteria, 11 (42.3%) patients had a definite diagnosis and 15 (57.7%) patients a probable diagnosis of AIH. Their median IAIHG score was 6 (6–7) points. All patients were treated with corticosteroids and the median time elapsing between hospital admission and the initiation of corticosteroid therapy was 11 (7–18) days. Regarding corticosteroids dose, 23 (88.5%) received a dose of 1 mg/kg/day, while 3 (11.5%) received a dose of 0.5 mg/kg/day. One patient was treated with dual therapy (prednisolone and azathioprine) as induction therapy. There were no patients under antibiotic prophylaxis. During treatment, 5 (19%) of patients developed infections [2 spontaneous bacterial peritonitis (SBP), 1 urinary infection and 2 respiratory infections)].

Overall, 19 (73%) patients had responded to corticosteroids, 5 (19.2%) underwent LT and 2 (7.8%) died from infectious complications (SBP and pneumonia). For patients underwent LT, the median time between steroid introduction and LT was 12 (6–25) days. The median time between the inscription on the waiting list and LT was 7 (3–9) days. For responders, the median follow-up time was 36 (18–50) months, 17 (89%) were under Azatioprine and 2 (11%) were under cyclosporin for incomplete response and Azatioprine intolerance, respectively. Table 1 provides a descriptive summary of the features of the 26 patients who met the criteria for AS-AIH.

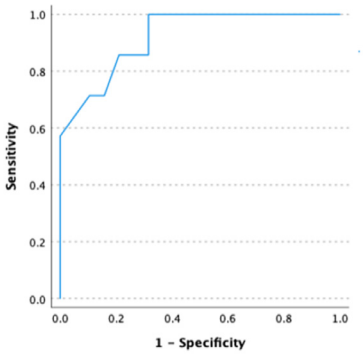
At admission, presence of ascites (0% vs. 42.9%, P:0.013) and HE (15.8% vs. 100%, $P<0.01$) were significantly higher for non-responders. Also, the median INR were superior for non-responders [(1.46 (1.3–1.58) vs. 2.12 (1.9–2.2), P:0.01]. There were no significant differences between responders and non-responders for creatinine [0.77 (0.58–0.93) vs. 0.79 (0.7–0.93), P: 0.401], bilirubin [14.1 (11–20.1) vs. 14.8 (7.7–19.6), P:0.59], MELD-Na$^+$ [23 (20–25) vs. 26 (22–29), P:0.08] and UKELD [61 (59–62) vs. 62 (59–74), P:0.26]. The interval between admission and the initiation of corticosteroids was not different between responders and non-responders [13 (7–23) vs. 8 (3–10), P:0.06], respectively. The initial dose of corticosteroids did not differ between responders and non-responders (1 mg/kg - 84.2% vs. 100%, P:0.264), respectively.

At time of corticosteroid initiation, presence of ascites (5.3% vs. 42.9%, P:0.04) and HE (15.8% vs. 100%, $P<0.01$) were significantly higher for non-responders. The median INR [1.38 (1.25–1.66) vs. 2.6 (1.88–2.82), $P<0.01$], UKELD [60 (59–61) vs. 63 (62–65), $P<0.01$) and MELD-Na$^+$ [23 (20–24) vs. 29 (26–31) $P<0.01$] were significantly lower in responders.



Cut-off	Sensitivity	Specificity	PPV	NPV
-2.5	85.7%	100%	100%	95%

Fig. 1. The optimal cut-off for the SURFASA score.
PPV: positive predictive value; NPV: negative predictive value.



Cut-off	Sensitivity	Specificity	PPV	NPV
26	85.7%	78%	60%	93.7%

Fig. 2. The optimal cut-off for the MELD-Na$^+$at third day of corticosteroid therapy.
PPV: positive predictive value; NPV: negative predictive value.

At third day of corticosteroid therapy, presence of ascites (5.3% vs. 42.9%, P:0.04) and HE (15.8% vs. 100%, $P<0.01$) were significantly higher for non-responders. The median INR [1.28 (1.21–1.49) vs. 2.86 (2.51–3.18), $P<0.01$], UKELD [60 (57–61) vs. 63 (62–65), $P<0.01$] and MELD-Na$^+$ [20 (18–25) vs. 29 (26–36), $P<0.01$] were significantly lower in responders. INR improvement after three days of corticosteroid therapy was superior for responders [−0.07 (−0.12–0.19) vs. 0.12 (0.03–0.34), P:0.04]. SURFASA score was significantly lower in the group of responders [−4,42 [−4,84- (−3,8)] vs. −1,85 [−2,35- (−1,85)].

Under multivariate analysis, MELD-Na$^+$ (D3) and SURFASA were independently associated with non-response to corticosteroids: MELD-Na$^+$ (D3) [Odds ratio (OR):1.4; 95% CI: 1–2.5; P:0.04)] and SURFASA score (OR: 7.4; 95% CI: 1.2–98; $P<0.01$). These results are summarized on Table 2.

SURFASA score had an excellent performance for predict therapeutic response (AUROC: 0.96 (0.87–1), $P<0.01$) as well as MELD-Na$^+$ at D3 (AUROC: 0.92 (0.81–0.99), $P<0.01$). For SURFASA, a score superior to −2.5 had sensitivity of 85.7%, specificity of 100%, PPV of 100% and NPV of 95% to rule out response to corticosteroids (Fig. 1). A MELD-Na$^+$ (D3) score superior to 28 had sensitivity of 85.7%, specificity of 78%, PPV of 60% and NPV of 93.5% to rule out corticosteroid response (Fig. 2). The pair-wise comparison of AUROC between SURFASA and MELD-Na$^+$ (D3) score did not show any significant differences (P-value > 0.05 for paired comparison).

Table 2
Analysis of factors associated with a non-response to corticosteroid therapy.

	Responders (n = 19)	Non responders (n = 7)	P-value	Multivariate analysis		
				OR	95% CI	P-value
At admission						
Ascites	0 (0%)	3 (42.9%)	0.013			
Hepatic Encephalopathy	3 (15.8%)	7 (100%)	<0.01			
Bilirubin	14.1 (11–20.1)	14.8 (7.7–19.6)	0.59			
Creatinine	0.77 (0.58–0.93)	0.79 (0.7–0.93)	0.401			
INR	1.46 (1.3–1.58)	2.12 (1.9–2.2)	0.01			
UKELD	61 (59–62)	62 (59–74)	0.26			
MELD-Na^+	23 (20–25)	26 (22–29)	0.08			
At time of corticosteroid therapy initiation (D0)						
Ascites	1 (5.3%)	3 (42.9%)	0.04			
Hepatic Encephalopathy	3 (15.8%)	7 (100%)	0.01			
Bilirubin	15.2 (11.9–24.2)	15.9 (13.2–20.9)	0.62			
Creatinine	0.78 (0.58–0.95)	0.91 (0.76–0.99)	0.3			
INR	1.38 (1.25–1.66)	2.6 (1.88–2.82)	0.01			
UKELD	60 (59–61)	63 (62–65)	<0.01			
MELD-Na^+	23 (20–24)	29 (26–31)	<0.01			
At third day of corticosteroid therapy (D3)						
Ascites	1 (5.3%)	3 (42.9%)	0.04			
Hepatic Encephalopathy	3 (15.8%)	7 (100%)	<0.01			
Bilirubin	11.3 (7.89–14.5)	19.7 (13.3–22.1)	0.11			
Creatinine	0.78 (0.54–0.98)	0.91 (0.76–0.99)	0.33			
INR	1.28 (1.21–1.49)	2.86 (2.51–3.18)	<0.01			
UKELD	60 (57–61)	65 (62–66)	<0.01			
MELD-Na^+	20 (18–25)	29 (26–36)	<0.01	1.4	1–2.5	0.04
SURFASA	−4,42 [−4,84- (−3,8)]	−1,85 [−2,35- (−1,85)]	<0.01	7.4	1.2–98	<0.01

4. Discussion

In the setting of AS-AIH a trial of corticosteroids with early evaluation of response is justified in almost all patients with AS-AIH, however there are still some uncertainties about the optimal management of these patients, namely types, dose, administration routes and early predictors of non-response [10,11]. It is also important to point out that there are no specific management guidelines for ALF or ACLF patients with AS-AIH [3]. The early identification of factors that are predictive of a non-response to corticosteroid therapy and suggestive of the need for LT is crucial. Compared to the acute setting of AIH, the time available for decision-making with AS-AIH is extremely short.

We reported a response rate of 73%. Our data were in line with the response rate described in literature, that varies between 57 and 82% [4,6,12,13].

Regarding clinical parameters, the presence of ascites and HE at presentation and their maintenance during corticosteroid therapy were significantly higher for non-responders. These clinical signs are expectable predictors of non-response as they reflect more severe disease [1]. Some studies demonstrated that HE is correlated with lower chance of responding to therapy, suggesting that attempting corticosteroid therapy in patients with low-grade HE should be discussed on a case-by-case basis [1].

We noticed our INR score at presentation was significantly lower than reported by De Martin et al. [38 (1.25–1.66) vs. 1.8 (1.6–2.2)] and by Lin et al. [1.99 ± 0.71 vs. 38 (1.25–1.66)] which reflects the heterogeneity of the population than can be included by the adopted definition of AS-AIH. However, as previously demonstrated, our study showed that higher INR score at presentation is associated with treatment failure, indicating that the prognosis of the patients depends, at least in part, on the initial disease severity [6,14].

INR, UKELD and MELD-Na^+at time of corticosteroids initiation were significantly higher for non-responders. These data were corroborated by previous studies [4,7,15]. One study reported that INR values with a cut-off point 2.46 before corticosteroid initiation were predictive of treatment failure [15]. Another study recorded AUROC curves for MELD-Na^+ (0.69, P: 0.03) and UKELD (AUC 0.70, P: 0.03) in predicting non-response at time of corticosteroids initiation [4].

At the third day of corticotherapy INR, UKELD and MELD-Na^+values were superior for non-responders. Our data were supported by De Martin *et al.* in the first study that described the possibility of predicting non-response as early as the third day.

The interval between presentation and corticosteroid initiation is similar between responders and non-responders, arguing in favour that additional factors other than the timing of corticosteroids determine the response to treatment, as previous demonstrated [4,15]. Also the initial dose of corticosteroid did not differ between responders and non-responders. These results were in line previous studies [6,10,13,15].

AS-AIH itself is associated with increased rates of infectious complications. In addition, corticosteroid exposure may propagate infections, although in previous studies corticosteroid therapy did not significantly increase the incidence of infection [16] It is important to analyse infectious complications in making the decision of LT. Infectious complications were present in 20% of our cohort, a value similar to reported in the literature [6,16].

Under multivariate analysis, MELD-$Na^+$and SURFASA can be used for predicting non-response. The AUROC of MELD-Na^+ (D3) for predicting outcome was 0.92 and the best cut-off was 28. Our findings were consistent with those of another study which had reported an AUROC for MELD-$Na^+$of 0.917, however with a cut-off of 26 [12]. Noguchi et al. described an AUROC for MELD-Na^+ (D7) of 0.89 at a cut-off of 20 and stated that MELD-Na^+at day 7 over 20 provides an easy-to-use and reliable prognostic predictor and guide for second-line drug initiation or for emergent LT [17]. Our results support the rational for shortening this watchful observation to 3 days. The AUROC of SURFASA for predicting outcome was 0.96, which was higher than previous described by De Martin et al. [6] and was in line with the described by Lin et al. [12].

In our cohort, the best cut-off value of SURFASA was −2.5, which was significantly lower than reported in the study by De Martin *et al.* [6] but was in line with the reported by Lin *et al.* [12] When the threshold was lowered to −2.5, the survival rate was 100% in the patients with SURFASA score inferior or equal to −2.5; 85.7% of those with SURFASA superior to −2.5 died or underwent LT. The AUROC of SURFASA for predicting outcome was higher than those of other models, however we did not find statistically difference between the SURFASA score and MELD-Na$^+$ (D3). Nevertheless, more prospective studies are necessary for further validation, namely, its calculation at different time intervals depending on the patient's characteristics [18].

We can point out some limitations to our study. Firstly, the simplified IAIHG score was used for stablishing the diagnosis. Its use does not appear to be satisfactory, even though it is widely applied in clinical practice. Secondly, although all patients performed liver biopsy before starting therapy, histological data were not reported in most patients, precluding the adequate evaluation of pathological features that could determine the response to steroids. Although it has been reported that in patients with AIH-related ACLF, fibrosis stage higher than 2 was correlated with an unfavourable response to corticosteroids, the predictive value of histological findings in AS-AIH is currently not clear. Thirdly, because there is no recognized definition a corticosteroid response in this setting, we decided to use the definition previously used by De Martin *et al.* [6]: LT-free survival at 90 days. Additionally, it is important to acknowledge that these data represent the experience of a selected patient population in tertiary referral centres with significant experience of managing complex presentations of AIH.

Concluding, SURFASA has been confirmed as a valuable tool for the early identification of patients who are non-responders to corticosteroids and require rapid evaluation for LT. Although, more prospective studies are necessary for further validation, we proved that MELD-Na$^+$ (D3) and SURFASA are reliable early prognostic predictors.

Conflict of interest

None declared.

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