



RESEARCH ARTICLE

REVISED Platelet count can predict the grade of esophageal varices in cirrhotic patients: a cross-sectional study [version 2; peer review: 2 approved]

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Abstract

Background: Bleeding from esophageal varices is a life-threatening complication in cirrhosis. Screening endoscopy is recommended in cirrhotic patients to identify patients at risk of variceal hemorrhage, but this is an invasive procedure and has limitations. Therefore, thrombocytopenia has been proposed to predict the existence and grade of esophageal varices. The aim of the current study was to determine a correlation between platelet count and grades of esophageal varices in patients with liver cirrhosis.

Methods: This cross-sectional study was conducted at the POF Hospital, Wah Cantt from 1st October, 2017 to 30th May, 2018. Newly diagnosed cases of cirrhosis having varices of any grade on endoscopy were included. Endoscopic findings of patients were standardized using Paquet grading system. On the basis of platelet count, patients were divided into four subgroups. Platelet count groups were correlated with grading of esophageal varices using Spearman rank correlations. Chi Square test was used to see association between the platelet count and grade of esophageal varices.

Results: 110 patients were included in the study, 55.5% (n=61) were male. Mean age of the patients was 59.89±9.01 years. Platelet count was <50,000/uL in 35.5% patients, 50,000-99,000/uL in 26.4%, 100,000-150,000 in 12.7%, and >150,000/uL in 25.5% patients. Grade I esophageal varices were found in 23.6% of patients, whereas grade II, III and IV were found in 24.5%, 33.6% and 18.2% of patients, respectively. Mean platelet count was 213884.62/mm³ in patients with grade I varices, whereas it was 119518.52/mm³, 58386.49/mm³ and 21600.00/mm³ in patients with grade II, III and IV varices, respectively (p<0.0001). A significant negative correlation between platelet count and grades of esophageal varices was found (p<0.001).

Open Peer Review

Reviewer Status

	Invited Reviewers	
	1	2
version 2		
(revision)		
24 Nov 2021	report	report
	↑	↑
version 1		
11 Feb 2021		
	report	report

1. **Muhammad Asim Anwar**, Pakistan Atomic Energy Commission, Islamabad, Pakistan
PAEC General Hospital, Islamabad, Pakistan
2. **Alexandru Constantin Moldoveanu** , Gastroenterology and Internal Medicine II Clinic - University Emergency Hospital Bucharest, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

Any reports and responses or comments on the article can be found at the end of the article.

Conclusion: Platelet count can predict the grade of esophageal varices in cirrhotic patients. There is significant negative correlation between platelet count and grades of esophageal varices.

Keywords

Cirrhosis, Platelet, Varices

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Author roles: **Afsar A:** Conceptualization, Investigation, Methodology, Resources, Software, Visualization, Writing – Original Draft Preparation; **Nadeem M:** Data Curation, Formal Analysis, Software, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Shah SAA:** Conceptualization, Project Administration, Resources, Supervision, Writing – Review & Editing; **Hussain H:** Data Curation, Investigation, Methodology, Resources; **Rani A:** Data Curation, Investigation, Methodology, Project Administration, Software; **Ghaffar S:** Investigation, Methodology, Resources, Software, Validation

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REVISED Amendments from Version 1

We had made few changes as suggested by reviewers. We applied one way ANOVA (Analysis of Variance) test and added in results. Reviewer raised an important point regarding the imminent bleeding signs, which we missed during data collection. As it is not possible to include it in article (we do not have data), we had mentioned it in limitations of our study in revised version so researchers in future can include this point. We added the some details of other non invasive methods in discussion as advised by reviewer.

Any further responses from the reviewers can be found at the end of the article

Introduction

Portal hypertension is a common complication of liver cirrhosis which can lead to esophageal varices that may rupture and bleed¹. Bleeding from esophageal varices is life threatening and comprises 10% of all cases of upper gastrointestinal (GI) bleeding². Esophageal varices are present in approximately one third of patients at diagnosis of cirrhosis and incidence increases to 90% in 10 years³. The rate of progression from small to large varices is estimated to be 8–10% per year and the annual rate of esophageal hemorrhage is 5% for small varices and 15% for large varices^{3,4}. Screening endoscopy is therefore recommended for early detection of esophageal varices and grading of varices in cirrhotic patients to identify patients with risk of variceal hemorrhage and administer prophylactic treatment if required⁵. Screening endoscopy is however an invasive procedure and has limitations⁶.

Diagnosis and grading varices by endoscopy is operator dependent. This approach also places a heavy burden upon endoscopy units and repeated testing over time may affect patient compliance, and endoscopic screening also increases the associated health care costs⁷. Due to these problems regarding endoscopy, some noninvasive means have been proposed for prediction of esophageal varices and their grades in order to restrict endoscopy to the population with high risk of variceal bleeding⁷. Various clinical and biochemical predictors have been studied to predict the existence and grade of esophageal varices in cirrhotic patients⁸.

Thrombocytopenia (platelet count <150,000 /uL) is one such predictor. It is found in approximately 64–76% of patients with portal hypertension and cirrhosis⁹. The pathogenesis of thrombocytopenia in cirrhosis is multi-factorial and includes decreased thrombopoietin production, sequestration of platelets in spleen and direct myelosuppression due to hepatitis C virus¹⁰. As thrombocytopenia and esophageal varices are common findings in cirrhosis, and portal hypertension is associated with both of these findings, some studies have been conducted to see the relation of thrombocytopenia as a non-invasive marker with grades of esophageal varices^{10,11}. It was found in different studies that platelet count was inversely correlated with grades of esophageal varices¹¹. Large esophageal varices also appeared to have a lower platelet count in a study conducted at Shanghai East Hospital⁴

In resource poor developing countries, endoscopy of every cirrhotic patient to grade the esophageal varices to select the patients for prophylactic therapy is not possible due to the limited number of endoscopes and endoscopists in government hospitals. We need to identify non-invasive and reliable markers to predict the grades of esophageal varices in our population in Pakistan, so that endoscopists can select the patients at increased risk of bleeding for endoscopy on priority basis. Therefore, we conducted this study to determine correlation between platelet count and grades of esophageal varices in our population and thus assess the possibility of using platelet count to predict the grades of esophageal varices.

Methods**Study design and participants**

This cross-sectional descriptive study was conducted at the Department of Medicine, POF Hospital, Wah Cantt, Pakistan from 1st October, 2017 to 30th May, 2018. Newly diagnosed cases of cirrhosis having varices of any grade on endoscopy, irrespective of the cause of cirrhosis, with or without ascites and splenomegaly, from 18 to 70 years were included in the study. Diagnosis of cirrhosis was made using data obtained from clinical findings, laboratory investigations and ultrasonographic findings of the liver. Patients with hematological disorders, portal vein thrombosis, on B-blocker prophylactic therapy and those who had undergone endoscopic band ligation or sclerotherapy were excluded.

The sample size calculated was 110 using sample size calculator $n = (Z^2 \times P \times (1 - P))/d^2$ for cross sectional studies, taking a confidence level 95%. In total, 110 patients were included by consecutive sampling.

Informed written consent was taken from patient or relative wherever relevant (consent was taken from relatives in patients with hepatic encephalopathy). Ethical approval was obtained from POF Hospital Research Ethics Committee before the start of the study (vide letter no. POFH/ERC/99053/03).

Data collection

Endoscopy was performed by the same endoscopist using the Olympus GIF type Q260 endoscope. All patients were kept NPO for 8 hours before endoscopy and the endoscopic findings of the patients were standardized using the Paquet grading system for esophageal varices dividing esophageal varices by grades I to IV¹². Blood samples of all patients were taken by the staff nurse before endoscopy and sent to the laboratory of POF Hospital on the same day to calculate platelet count. Platelet count was calculated by automatic hematology analyzer (Sysmex XN-1000) and confirmed by manual method (small volume of whole blood was treated with RBC lysing reagent ammonium oxalate, was put in hemocytometer and platelet counting was done by hematologist using phase contrast light microscopy). All details including demographic details, endoscopic findings and platelet count were obtained from medical records of the selected patients. On the basis of platelet count, patients were divided into four subgroups: group 1, platelet count

<50,000/uL; group 2,platelet count 50,000–99000 /uL; group 3,platelet count 100,000–150,000/uL; and group 4,normal platelet count >150,000/uL.

Data analysis

All data was entered and analyzed using SPSS version 19.0. Mean and standard deviation was calculated for quantitative data, such as age. Frequency and percentage was calculated for gender, platelet count and grade of esophageal varices. Platelet count group was correlated with grading of esophageal varices using Spearman rank correlations. Chi square test was used to calculate the association between platelet count and grade of esophageal varices. P-value ≤0.05 was considered significant.

Results

A total of 110 patients were included in the study, 55.5% (n=61) were male and 44.5% (n=49) were female. Mean age of the patients was 59.89±9.01 years. Platelet count was <50,000 /uL in 35.5% (n=39) of patients, 50,000–99,000/uL in 26.4% (n=29), 100,000–150000 in 12.7% (n=14), and >150,000/uL in

25.5% (n=28) patients. Grade I esophageal varices were found in 23.6% (n=26) patients, whereas grade II, grade III and grade IV were found in 24.5% (n=27), 33.6 (n=37) and 18.2% (n=20) of patients, respectively.

A significant association was found between the platelet count groups and grades of esophageal varices; groups with lower platelet counts had high-grade varices, while groups with higher platelet counts had low-grade varices (Table 1).

Spearman’s correlation showed a significant negative correlation between platelet count and grades of esophageal varices (Table 2).

Mean platelet count was also significantly lower in patients with grade IV varices as compared to patients with grade I varices (p=0.0001; Table 3).

Analysis of variance also showed significant relation between platelet count and grades of esophageal varices. (p <0.0001; Table 4; Figure 1).

Table 1. Association of platelet count group with grades of esophageal varices.

Platelet count		Paquet variceal grade				Total	p-value
		I	II	III	IV		
<50,000/uL	Group 1	2	3	16	18	39	<0.001
50,000–99,000/uL	Group 2	1	9	17	2	29	
100,000–150000/uL	Group 3	1	9	4	0	14	
> 150,000/uL	Group 4	22	6	0	0	28	

Table 2. Correlation of platelet count with grades of esophageal varices.

		Platelet count	Grades of esophageal varices
Spearman's Rho	Platelet count	Correlation coefficient	1.000
		p-value	/
	Paquet variceal grade	Correlation coefficient	-0.783
		p-value	<0.001

Table 3. Association of mean platelet count with Paquet variceal grade.

Paquet variceal grade	Mean platelet count (mm ³)	Std. deviation (mm ³)	N	p-value
I	213884.62	86434.867	26	<0.001
II	119518.52	68027.919	27	
III	58386.49	34188.433	37	
IV	21600.00	16161.683	20	

Table 4. Platelets count and esophageal varices relation.

	Sum of Squares	df	Mean Square	F	p value
Between Groups	5.332E+11	3	1.777 E+11	53.197	<0.0001
Within Groups	3.541 E+11	106	3340931677.643		
Total	8,873 E+11	109			

Lower platelet count is significantly associated higher grades of esophageal varices.

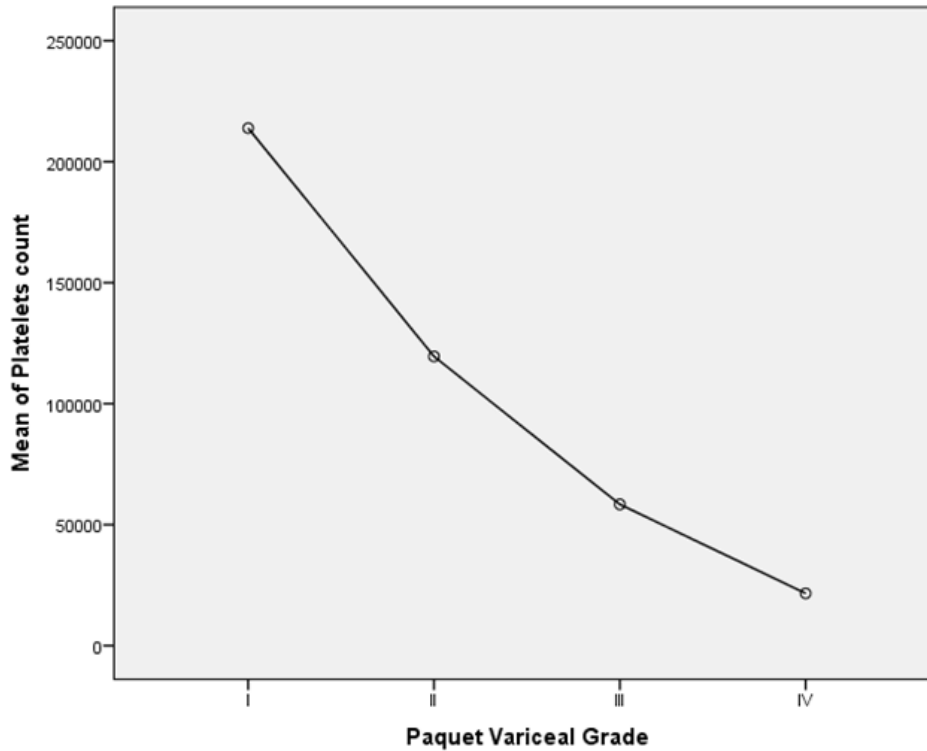


Figure 1. Graphical representation also shows that lower platelet count is significantly associated with higher grades of esophageal varices (Analysis of variance).

Discussion

Our results showed that there is a significant negative correlation between the platelet count and grades of esophageal varices. Patients with a lower platelet count had varices of higher grades. In group 1 patients (platelet count <50,000/uL; n=39), 18 and 16 patients were found to have grade IV and grade III varices, respectively, as compared to only 2 and 3 patients having grade I and II varices, respectively. In contrast, in group 4 patients (platelet count >150,000/uL; n=28), 22 patients had grade I varices and no patients had grade III or IV varices. This suggests that platelet count can be used as a predictor of grades of esophageal varices without frequent upper GI endoscopy.

In our study, 55.5% (n=61) patients were male and 44.5% (n=49) were female. Studies have shown that the incidence of cirrhosis is lower in females as compared to males due to slower progression of fibrosis¹³. In a study conducted in Taiwan, 71% cirrhotic patients were male¹⁴. These findings are consistent with

our findings of male predominance. Another study also supports our findings, as it shows that men had a higher incidence of cirrhosis in all age groups as compared to women of the same age group¹⁵. A local study also showed that 64% of cirrhosis patients were men¹⁶.

Mean age in our study was 59.89±9 years. Although cirrhosis of the liver can develop at any age, it is usually common in old age with a higher mean age of incidence¹⁵. Mean age was found to be 40.5 years in cirrhosis patients in a study conducted by Devrajani *et al.*¹⁶. This is comparable with our results. A study conducted in China showed a mean age of 50.29±7.03 years in cirrhosis patients¹⁷, which is similar to a mean age of 54.39±7.46 years in a study conducted by Abd-Elsalam *et al.*¹⁰, almost the same mean age as found in our study.

A significant inverse correlation was found between platelet count and grades of esophageal varices in our study. Lower

platelet count was associated with high varices and vice versa. Platelet count is low in advanced cirrhosis; similarly, large varices are associated with advanced cirrhosis. Many studies conducted previously to see the relationship of platelet count with esophageal varices concluded that lower platelet count is associated with large varices. For example, a study conducted by Abbasi *et al.* shows that platelet count is inversely related with esophageal varices, supporting our findings¹¹. Similarly, a study conducted in India also had the same results; lower platelet count was significantly associated with large varices¹⁸.

Mean platelet count was significantly lower in patients with grade III ($58386.49 \pm 34188.43 \text{ mm}^3$) and IV ($21600.00 \pm 16161.68 \text{ mm}^3$) esophageal varices as compared to grade I ($213884.62 \pm 86434.86 \text{ mm}^3$) and II ($119518.52 \pm 68027.91 \text{ mm}^3$) varices in our study. These results are comparable with a study conducted in Egypt, where platelet count was significantly lower in patients with grades II and III (165.2 ± 13.0 and $60.3 \pm 14.1 \text{ mm}^3$, respectively) than in patients with grade I ($100.5 \pm 19.8 \text{ mm}^3$)¹⁹. According to these findings, platelet count can be used to identify patients who may have large varices and need prophylactic endoscopic treatment to prevent upper GI bleeding rather than doing endoscopy in every patient with cirrhosis.

Many studies earlier used platelet count along with other non-invasive parameters like platelet count/ spleen diameter ratio, AST Platelet Ratio Index (APRI) to predict the grades of esophageal varices and need of endoscopy in cirrhotic patients²⁰. It was found that these markers were useful in predicting the grades of esophageal varices^{20,21}. We only used

platelet count, platelet count is not only non-invasive, it is also inexpensive, resource effective, does not need special expertise, and is easily available.

Our study has some limitations: it was a single center study including all patients of cirrhosis irrespective of the cause; we only used platelet count to predict the grade of varices, some studies have shown that platelet count and spleen size ratio is more accurate in predicting the size and grade of varices. We did not look for impending or recent bleeding signs like cherry red spots along with grades of varices. In future, multicentre studies with specific cause of cirrhosis, using imminent bleeding signs also along with grades of varices and using platelet count and spleen size ratio are suggested.

Conclusion

There is significant negative correlation between platelet count and grades of esophageal varices. Low platelet count is associated with higher grades of esophageal varices. This suggests that platelet count can be used as a predictor to predict the grade of esophageal varices.

Data availability

Underlying data

Figshare: Platelet count can predict the grade of esophageal varices in cirrhotic patients, <https://doi.org/10.6084/m9.figshare.13379939.v1>²².

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

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Version 2

Reviewer Report 04 January 2022

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i have no further comments to make.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: internal medicine/gastroenterology/hepatology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 04 January 2022

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Alexandru Constantin Moldoveanu

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The second version of the article adds more context to the research, including limitations of the study which will be useful for future research in this field. A more thorough statistical analysis was performed, which further supports the conclusions of the article.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Gastroenterology, Gastrointestinal Endoscopy, Hepatology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 20 August 2021

<https://doi.org/10.5256/f1000research.30974.r90353>

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Alexandru Constantin Moldoveanu 

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Esophageal varices are a frequent complication of cirrhosis and can be a life-threatening complication if ruptured. The risk of variceal bleeding is, however, not equal between patients, and the current gold standard method for assessing bleeding risk is upper gastrointestinal endoscopy - an invasive procedure, that is not easily tolerated by the patient. There are multiple non-invasive methods that were proposed over the years as either an alternative to endoscopy or as a method of reducing the number of endoscopies by performing them selectively only in patients with a high probability of also requiring endoscopic treatment.

The authors' study presents a very simple parameter, thrombocyte count, as a non-invasive and very cost-effective alternative method of identifying patients with different grades of esophageal varices. Considering that both hypersplenism (and thrombocytopenia) and esophageal varices are results of portal hypertension, it appears to be a reasonable presumption that the two would be correlated.

The results indeed show as a very good correlation between the size of varices and platelet count, in both group analysis as well as continuous variable analysis. What is most interesting to me is that the platelet count has a very good sensitivity (approximately 93% based on the results) for predicting patients with large varices (grades III and IV) requiring prophylactic endoscopic treatment. No patient with normal thrombocytes has had large varices in this study, which suggests that these patients might not require diagnostic endoscopy.

Regarding the statistical analysis methodology, I believe that the methods could be expanded upon. An analysis of variance type test between groups would probably reveal statistically significant results given the values presented. Another possible analysis method is classifying patients into two groups: 1. needing endoscopic treatment and 2. not needing endoscopic treatment, and plotting an ROC curve, which could be used to determine sensitivity and specificity

for an optimal cut-off.

One criticism that I could make is that imminent bleeding signs, such as red wale signs, were not assessed. While these signs appear more frequently in large varices, they have frequently been reported in grade 2 varices as well, making it more difficult to assess which patients do not require endoscopy using the grade of the varices alone.

Another criticism of the article is that, while the conclusions are very interesting, the information is not entirely new. The Baveno VI consensus has already proposed thrombocyte count as one of the most important factors to determine which patients can be ruled out from screening endoscopy. The authors' study still has practical value for medical centres where measurement of the other main parameter in the Baveno VI consensus, liver stiffness, is either unavailable or not sufficiently cost-effective.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Gastroenterology, Gastrointestinal Endoscopy, Hepatology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 11 Nov 2021

Muhammad Nadeem, Poonch Medical College, Rawalakot, Pakistan

We would like to thank the reviewer for his valuable time and comments on our article; this will be very helpful for us in future research. We had made few changes as suggested by reviewer.

1. We applied one way ANOVA (Analysis of Variance) test and added in results.
2. Reviewer raised an important point regarding the imminent bleeding signs, which we missed during data collection. As it is not possible to include it in article (we do not have data), we had mentioned it in limitations of our study in revised version so researchers in future can include this point.

Another concern of reviewer was "information is entirely not new". We agree with this statement but most of the studies used other parameters as well along with platelet count like spleen diameter, liver stiffness as mentioned by reviewer also. We used only platelet count to predict the varices size which is valuable for centres in developing world where other facilities are not available or cost is a problem, this was the main purpose of the study and also appreciated by reviewer.

Competing Interests: No competing interests were disclosed.

Reviewer Report 30 June 2021

<https://doi.org/10.5256/f1000research.30974.r87611>

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In this cross sectional of the platelet count predictability of esophageal varix is important study for those countries where the availability of the endoscopy services are few and the burden of disease is high. You can also schedule the endoscopy procedure where the predictability of high grade varix is high. Methodology is fine and the results are also presented well. In the discussion authors should also give some details of other non invasive methods like platelet spleen index. In conclusion there is significant negative correlation between platelet count and grade of varix

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: internal medicine/gastroenterology/hepatology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 11 Nov 2021

Muhammad Nadeem, Poonch Medical College, Rawalakot, Pakistan

We would like to thank the reviewer for his valuable time and comments on our article; this will be very helpful for us in future research.

We added the some details of other non invasive methods in discussion as advised by reviewer

Competing Interests: No competing interests were disclosed.

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