DANISH MEDICAL JOURNAL

Original Article

Dan Med J 2021;68(9):A09200689

Limited value of preoperative neutrophil-to-lymphocyte ratio to predict post-operative outcomes after major emergency abdominal surgery

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Dan Med J 2021;68(9):A09200689

ABSTRACT

INTRODUCTION Major emergency abdominal surgery results in a high risk of morbidity and mortality. Preoperative neutrophil-to-lymphocyte ratio (NLR) has been proposed as a predictor of post-operative outcomes in elective surgery. The aim of the present study was to examine whether preoperative NLR was associated with post-operative morbidity and mortality after major emergency abdominal surgery.

METHODS We conducted a retrospective cohort study of patients undergoing major emergency abdominal surgery in two university hospitals in Denmark between 2010 and 2016. Associations between preoperative NLR and 30-day post-operative complications and mortality were established through multivariate logistic regression and receiver-operating characteristics (ROC) analysis.

RESULTS A total of 570 patients were included in the study. The overall 30-day mortality was 9.3% and 59.3% had post-operative complications. The median preoperative NLR was 8.6 (interquartile range: 4.8-14.7). Although NLR was higher in the group of patients who had complications or died after surgery, a multivariate analysis showed that the NLR was not associated with 30-day post-operative complications (odds ratio (OR) = 1.01 (95% confidence interval (CI): 0.99-1.02); p = 0.424) or mortality (OR = 0.99 (95% CI: 0.97-1.02); p = 0.57). The ROC analysis showed an area under the curve of 0.55 and 0.60 for 30-day post-operative complications and mortality, respectively.

CONCLUSIONS Preoperative NLR was not associated with 30-day post-operative complications and mortality in patients undergoing major emergency abdominal surgery.

FUNDING none.

TRIAL REGISTRATION not relevant.

Patients undergoing major emergency abdominal surgery have a high risk of post-operative complications and mortality. Major emergency abdominal surgery represents 12.5% of all surgical procedures but is responsible for more than 80% of post-operative deaths [1-5].

After major emergency abdominal surgery, predictors of adverse post-operative outcomes are important for optimising pre-, peri- and post-operative intensive care and treatment and supporting clinical decisions.

The neutrophil-to-lymphocyte ratio (NLR) is an inflammatory marker, which is inexpensive, highly available and reproducible. Studies have shown that increasing NLR is associated with systemic inflammation and physical stress and serves as a prognostic factor for patients with various types of cancers, including pancreatic cancer, colorectal cancer and various types of hepatic cancers [6-9].

Preoperative NLR has been shown to be useful in predicting mortality and post-operative complications in patients undergoing elective major vascular surgery [10] and hepatic resection for colorectal liver metastasis [7].

Preoperative NLR has been higher in patients with intestinal obstruction in need of surgery than in conservatively treated patients [11]. Likewise, preoperative NLR was significantly higher in patients with surgically treated incarcerated groin hernia than in conservatively treated patients [12]. These findings indicate that NLR is increased during acute abdominal pathology and that it may potentially correlate with the severity of the abdominal pathology.

The prognostic value of preoperative NLR in patients undergoing major emergency abdominal surgery has not previously been examined in a large cohort. We hypothesised that a high NLR in patients undergoing major emergency abdominal surgery was associated with an increased risk of post-operative complications and mortality. Therefore, this study aimed to determine the association between preoperative NLR and 30-day post-operative complications and mortality in patients undergoing major emergency abdominal surgery.

METHODS

Study population and design

Patients undergoing major emergency abdominal surgery at Zealand University Hospital, Denmark, from 2010 to 2016 and at Herlev Hospital, Denmark, from 2009 to 2013 were retrospectively included in the study. Patients were selected by screening the operation lists by International Classification of Diseases, tenth version (ICD-10) procedure codes. **Appendix 1 (https://ugeskriftet.dk/files/a09200689_-_supplementary.pdf)** shows inclusion by ICD-10 procedure codes. The inclusion criteria were a preoperative NLR, age > 17 years and major surgery on the gastrointestinal tract performed within 72 hours of admission to the department of surgery or as an acute reoperation after an elective procedure. If multiple procedures were performed on different anatomical sites within the abdominal/pelvic cavity, the patient would be included provided the major procedure was general surgery. The exclusion criteria were minor surgery, which included 1) diagnostic laparoscopy where no subsequent procedure was performed, 2) appendectomy, 3) cholecystectomy, 4) hernia repair without bowel resection, 5) minor abdominal wound dehiscence and 6) pathology due to pregnancy, pathology caused by trauma and pathology of the oesophagus, spleen, renal tracts, kidneys, liver, gall bladder and biliary tree, pancreas or urinary tract. In all, 376 patients with no preoperative NLR assessment were excluded.

The patient charts were studied from admission to in-hospital death or up to 30 days after surgery. When the patient had been discharged before post-operative day 30, the electronic patient chart was examined for any readmission to the hospital for conditions related to abdominal pathology or the surgical procedure, thereby obtaining a complete 30-day follow-up. Patient demographic and preoperative data were collected retrospectively through patient charts, including but not limited to age, gender, American Society of Anesthesiologists (ASA) score (defined by anaesthesiologists), and the Charlson Comorbidity Index (CCI). Perioperative data included type of surgery (upper gastrointestinal surgery, small bowel resection, large bowel resection, laparotomy without resection, small and large bowel resection, and other types of surgery to the gastrointestinal tract). Laparotomy without resection included exploratory laparotomy with bowel obstruction and/or adhesiolysis without any bowel resection. Post-operative complications were defined by the Clavien-Dindo Classification, which was assessed retrospectively by the investigators based on data from the electronic

patient charts.

The study was approved by the Danish Data Protection Agency (REG-010-2017 and HEH-2013-034).

Statistical analysis

Categorical data were reported as n (%) and compared across groups by the χ^2-test. Numerical data were presented as mean (standard deviation, SD) or median (interquartile range, IQR) where appropriate and compared across groups by the Student's t-test or the Mann-U Whitney test. Multivariate logistic regression analyses were performed to study the associations between NLR and post-operative outcomes such as reoperations, complications and mortality. The analyses on post-operative complications included the following predefined variables: gender, age, ASA score and type of surgery. The analyses on 30-day mortality included the following predefined variables: gender, age, ASA score, type of surgery and NLR.

The values of neutrophils and lymphocytes were processed as continuous numerical data with no cut-off value. The predictive value of NLR was examined using receiver-operating characteristics (ROC) curve analysis. The predicted probability from the best model was used to generate the curves and to present the area under the curve (AUC), sensitivity and specificity. A two-sided p-value < 0.05 was considered statistically significant.

The study was reported in accordance with the STROBE statement [13].

Trial registration: not relevant.

RESULTS

Study population and demographics

A total of 570 patients were included in the study. Among these, 322 were female (57%), the mean age was 65 years (SD: ± 17 years), 153 (26.8%) had an ASA score > 2 and 163 (28.6%) had a CCI ≥ 2. The majority underwent an open procedure (n = 381 (66.8%)), and the primary type of surgery was laparotomy without resection (45.4%). See **Table 1** for baseline characteristics.

TABLE 1 Baseline characteristics stratified by 30-day post-operative complications.

	Without (n = 232)	With (n = 338)	Total (N = 570)	p-value
NLR, median (IQR)	8.2 (4.8-12.0)	9.1 (5.0-16.5)	8.6 (4.8-14.7)	0.05
Age, mean (± SD), yrs	59.2 (± 18.2)	68.9 (± 14.4)	64.9 (± 16.7)	< 0.001
Gender, n (%)				0.26
Female	124 (53.4)	198 (58.6)	322 (56.5)	
Male	108 (46.6)	140 (41.4)	248 (43.5)	
BMI				
Mean (± SD), kg/m²	25.0 (± 6.1)	25.2 (± 5.4)	25.1 (± 5.7)	0.76
Missing, n (%)	68 (29.3)	87 (25.7)	155 (27.2)	
CCI, n (%)				< 0.001
0	139 (59.9)	131 (38.8)	270 (47.4)	
1	46 (19.8)	91 (26.9)	137 (24.0)	
2	21 (9.1)	50 (14.8)	71 (12.5)	
> 2	26 (11.2)	66 (19.5)	92 (16.1)	
ASA score, n (%)				< 0.001
I	57 (24.6)	50 (14.8)	107 (18.8)	
II	124 (53.4)	151 (44.7)	275 (48.3)	
III	33 (14.2)	104 (30.8)	137 (24.0)	
> III	5 (2.2)	11 (3.)	16 (2.8)	
Missing	13 (5.6)	22 (6.5)	35 (6.1)	
Smoking, n (%)				0.11
No	170 (73.3)	225 (66.6)	395 (69.3)	
Yes	62 (26.7)	113 (33.4)	175 (30.7)	
Alcohol abuse, n (%)				0.07
No	209 (90.1)	288 (85.2)	497 (87.2)	
Yes	16 (6.9)	40 (11.8)	56 (9.8)	
Missing	7 (3.0)	10 (3.0)	17 (3.0)	
Type of surgery, n (%)				< 0.001
Upper GI	8 (3.4)	31 (9.2)	39 (6.8)	
Small-bowel resection	50 (21.6)	68 (20.1)	118 (20.7)	
Large-bowel resection	15 (6.5)	74 (21.9)	89 (15.6)	
Laparotomy with/without resection	135 (58.2)	124 (36.7)	259 (45.4)	
Small + large bowel resection	12 (5.2)	34 (10.1)	46 (8.1)	
Other	12 (5.2)	7 (2.1)	19 (3.3)	
Open surgery, n (%)				0.31
Yes	149 (64.2)	232 (68.6)	381 (66.8)	
No	83 (35.8)	106 (31.4)	189 (33.2)	
30-day mortality, n (%)				< 0.001
No	230 (99.1)	287 (84.9)	517 (90.7)	
Yes	2 (0.9)	51 (15.1)	53 (9.3)	
Post-operative reoperation, n (%)				< 0.001
No	221 (95.3)	205 (60.7)	426 (74.7)	
Yes	11 (4.7)	133 (39.3)	144 (25.3)	

ASA = American Society of Anesthesiologists; CCI = Charlson Comorbidity Index; GI = gastrointestinal; IQR = interquartile range; NLR = neutrophil-to-lymphocyte ratio; SD = standard deviation.

The majority of the patients had post-operative complications according to the Clavien-Dindo Classification (n = 338 (59.3%)), and 144 (25.3%) were reoperated. The overall 30-day mortality was 9.3% (n = 53).

The neutrophil-to-lymphocyte ratio

The overall median NLR value was 8.6 (IQR: 4.8-14.7). Patients who developed post-operative complications had a higher preoperative NLR than patients without complications (9.1 (IQR: 5.0-16.5) versus 8.2 (IQR: 4.8-12.0), p = 0.05). Patients who died within 30 days of surgery had a significantly higher NLR than patients who survived (10.1 (IQR: 6.6-18.8) versus 8.3 (IQR: 4.7-14.2)), p = 0.02). Patients with a post-operative complication were

significantly older, had a higher CCI and ASA score, and had more comprehensive surgery (Table 1). The rate of post-operative complications was higher among patients who died within 30 days of surgery than among patients who survived beyond 30 days (55.5% versus 96.2%, p = 0.0001). Patients who died within 30 days of surgery were significantly older, had a higher CCI and had more comprehensive surgery than patients who survived (**Table 2**).

TABLE 2 Baseline characteristics stratified by 30-day mortality.

	Survived (n = 517)	Deceased (n = 53)	Total (N = 570)	p-value
Neutrophil concentration, mean (± SD), × 10^9/l	10.3 (± 5.4)	11.9 (± 6.8)	10.5 (± 5.6)	0.04
Lymphocyte concentration, mean (± SD), × 10^9/l	1.5 (± 5.2)	1.1 (± 0.8)	1.5 ± (5)	0.57
NLR, median (IQR)	8.3 (4.7-14.2)	10.1 (6.6-18.8)	8.6 (4.8-14.7)	0.02
Age, mean (± SD), yrs	63.6 (± 16.8)	77.7 (± 9.1)	64.9 (± 16.7)	< 0.001
Gender, n (%)				0.68
Female	294 (56.9)	28 (52.8)	322 (56.5)	
Male	223 (43.1)	25 (47.2)	248 (43.5)	
BMI				
Mean (± SD), kg/m²	25.2 (± 5.7)	24.2 (± 5.5)	25.1 (± 5.7)	0.34
Missing, n (%)	140 (27.1)	15 (28.3)	155 (27.2)	
CCI, n (%)				< 0.001
0	261 (50.5)	9 (17.0)	270 (47.4)	
1	125 (24.2)	12 (22.6)	137 (24.0)	
2	62 (12.0)	9 (17.0)	71 (12.5)	
> 2	69 (13.3)	23 (43.4)	92 (16.1)	
ASA score, n (%)				< 0.001
1	105 (20.3)	2 (3.8)	107 (18.8)	
2	260 (50.3)	15 (28.3)	275 (48.3)	
3	109 (21.1)	28 (52.8)	137 (24.0)	
> 3	11 (2.1)	5 (9.4)	16 (2.8)	
Missing	32 (6.2)	3 (5.7)	35 (6.1)	
Smoking, n (%)				0.81
No	357 (69.1)	38 (71.7)	395 (69.3)	
Yes	160 (30.9)	15 (28.3)	175 (30.7)	
Alcohol abuse, n (%)				0.75
No	450 (87.0)	47 (88.7)	497 (87.2)	
Yes	52 (10.0)	4 (7.6)	56 (9.8)	
Missing	15 (3.0)	2 (3.7)	17 (3.0)	
Type of surgery, n (%)				0.47
Upper GI	32 (6.2)	7 (13.2)	39 (6.8)	
Small-bowel resection	106 (20.5)	12 (22.6)	118 (20.7)	
Large-bowel resection	81 (15.7)	8 (15.1)	89 (15.6)	
Laparotomy with/without resection	237 (45.8)	22 (41.5)	259 (45.4)	
Small + large-bowel resection	43 (8.3)	3 (5.7)	46 (8.1)	
Other	18 (3.5)	1 (1.9)	19 (3.3)	
Open surgery, n (%)				0.21
Yes	341 (66.0)	40 (75.5)	381 (66.8)	
No	176 (34.0)	13 (24.5)	189 (33.2)	
Post-operative complications, n (%)				< 0.001
No	230 (44.5)	2 (3.8)	232 (40.7)	
Yes	287 (55.5)	51 (96.2)	338 (59.3)	
Post-operative reoperation, n (%)				0.007
No	395 (76.4)	31 (58.5)	426 (74.7)	
Yes	122 (23.6)	22 (41.5)	144 (25.3)	

ASA = American Society of Anesthesiologists; CCI = Charlson Comorbidity Index; GI = gastrointestinal; IQR = interquartile range; NLR = neutrophil-to-lymphocyte ratio; SD = standard deviation.

In the multivariate analyses, NLR was neither associated with post-operative complications (odds ratio (OR) = 1.01 (95% confidence interval (CI): 0.99-1.02); p = 0.42), nor with 30-day mortality (OR = 0.99 (95% CI: 0.97-1.02); p = 0.57), **Table 3** and **Table 4**. In the ROC curve analysis of NLR versus 30-day post-operative complications, the AUC was 0.55 (95% CI: 0.50-0.60), sensitivity 0.32 and specificity 0.81, **Figure 1**A. The AUC for NLR versus 30-day

mortality was 0.60 (95% CI: 0.52-0.68), sensitivity 0.66 and specificity was 0.54, Figure 1B.

TABLE 3 Multivariate logistic regression analysis on the association between neutrophil-to-lymphocyte ratio and 30-day post-operative complications.

	Odds ratio (95% CI)	p-value
NLR	1.01 (0.99-1.02)	0.42
Gender		
Female	Reference	
Male	0.85 (0.58-1.26)	0.42
Age group		
< 65 yrs	Reference	
65-80 yrs	1.71 (1.10-2.65)	0.02
> 80 yrs	2.15 (1.22-3.81)	0.008
ASA score		
1	Reference	
2	1.61 (0.96-2.70)	0.07
3	3.75 (2.00-7.03)	< 0.001
> 3	2.40 (0.70-8.22)	0.16
Type of surgery		
Upper GI	Reference	
Small-bowel resection	0.38 (0.15-0.93)	0.04
Large-bowel resection	1.67 (0.62-4.55)	0.31
Laparotomy with/without resection	0.26 (0.11-0.62)	0.002
Small + large-bowel resection	1.23 (0.41-3.69)	0.72
Other	0.21 (0.06-0.76)	0.02

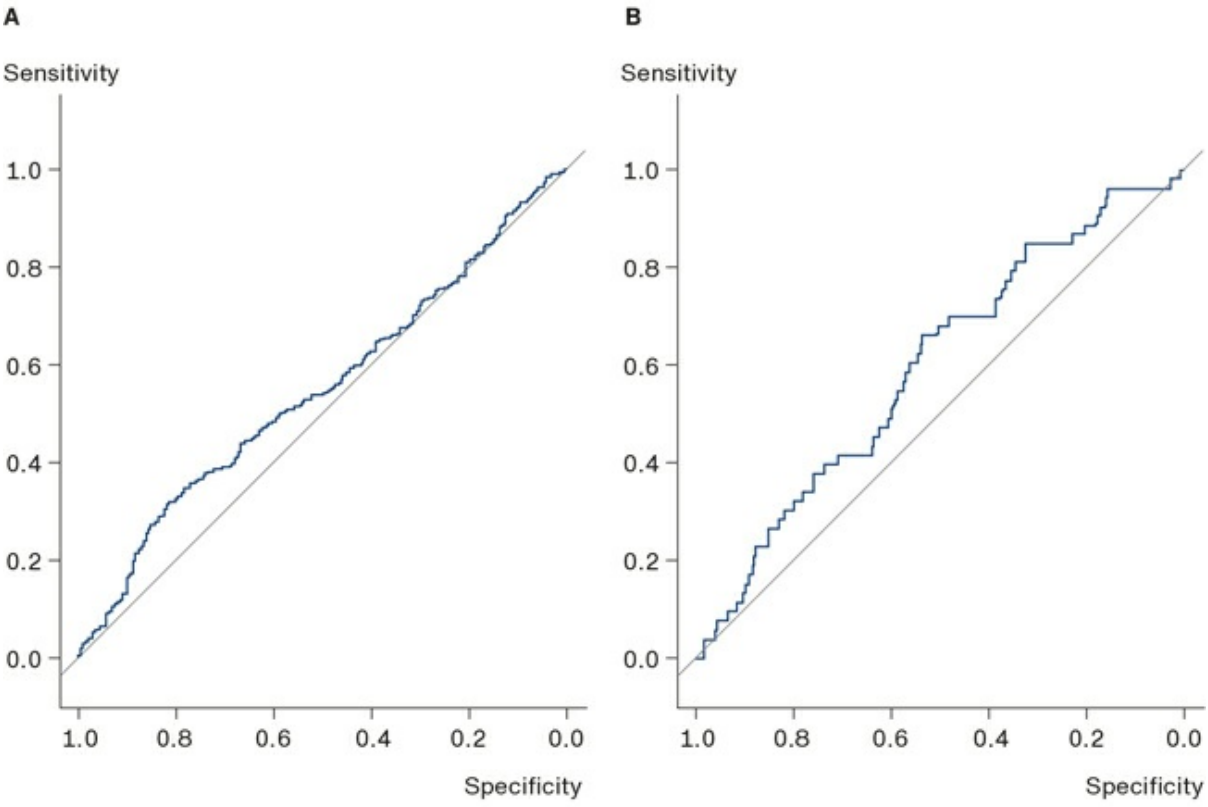
ASA = American Society of Anesthesiologists; CI = confidence interval; GI = gastrointestinal; NLR = neutrophil-to-lymphocyte ratio.

TABLE 4 Multivariate logistic regression analysis on the association between neutrophil-to-lymphocyte ratio and 30-day mortality.

	Odds ratio (95% CI)	p-value
NLR	0.99 (0.97-1.02)	0.57
Gender		
Female	Reference	
Male	1.40 (0.74-2.67)	0.30
Age group		
< 65 yrs	Reference	
65-80 yrs	5.24 (1.73-15.92)	0.003
> 80 yrs	10.77 (3.45-33.62)	< 0.001
ASA score		
1	Reference	
2	1.85 (0.40-8.57)	0.43
3	6.37 (1.49-30.45)	0.01
> 3	10.67 (1.73-65.86)	0.01
Type of surgery		
Upper GI	Reference	
Small-bowel resection	0.68 (0.23-2.03)	0.48
Large-bowel resection	0.56 (0.17-1.89)	0.35
Laparotomy with/without resection	0.45 (0.16-1.26)	0.13
Small + large-bowel resection	0.33 (0.06-1.97)	0.23
Other	0.39 (0.04-4.01)	0.57

ASA = American Society of Anesthesiologists; CI = confidence interval; GI = gastrointestinal; NLR = neutrophil-to-lymphocyte ratio.

FIGURE 1 A. Receiver-operating characteristic curve analysis of neutrophil-to-lymphocyte ratio versus 30-day post-operative complications. **B.** Receiver-operating characteristic curve analysis of neutrophil-to-lymphocyte ratio versus 30-day mortality.



DISCUSSIONS

In this retrospective cohort study, we found that patients who developed post-operative complications had a higher preoperative NLR than patients without complications. Likewise, patients who died within 30 days of surgery had a significantly higher NLR than patients who survived. However, in the multivariate analyses, NLR was neither associated with post-operative complications nor with 30-day mortality.

Previous studies have found that pre-treatment NLR is a useful predictor for post-treatment outcomes and mortality, for example, in myocardial injury in patients undergoing non-cardiac surgery [14], in patients with acute coronary syndrome [15] and as a risk indicator for all-cause mortality in an elderly population [16]. Furthermore, a systematic review and meta-analysis of NLR in patients with colorectal cancer found elevated pre-treatment NLR to be an independent predictor of survival [6].

NLR has been suggested as an independent predictor of 30-day mortality among patients aged >80 years undergoing emergency abdominal surgery [17]. In that study, a NLR ≥ 22 was shown to be the best predictor of a 30-day outcome. The mortality rate was 31% at post-operative day 30, and patients had a higher degree of comorbidity than in our study. Furthermore, they included patients undergoing minor emergency abdominal surgery such as appendectomy and hernia repair, which were excluded from our study. Regarding major elective abdominal surgery, another study found no association between preoperative NLR and post-operative complications [18]. However, their results showed that NLR measured at post-operative day seven was a

prognostic factor for post-operative complications in the first post-surgical month.

One reason for our negative finding regarding NLR as a predictor for 30-day post-operative complications and mortality may be that NLR is already high when patients are admitted to the hospital due to the underlying acute inflammation. The inflammatory stress response behind the underlying disease in patients who will later undergo major emergency abdominal surgery may potentially explain a high NLR at admission. In the meta-analysis, the cut-off value for high NLR was ≥ 3 in two studies, ≥ 4 in three studies and ≥ 5 in the remaining eight studies [6]. In our study, the median NLR for all patients was 8.6. This may indicate that NLR is too high due to the acute inflammation so that it cannot be used as a prognostic factor.

In our study, more than half of the patients had at least one post-operative complication. Other studies report 70% of patients undergoing major emergency abdominal surgery with at least one post-operative complication, and the majority of these occurred between 72 hours and 30 days after surgery [4]. They found a 30-day mortality of 20%. Another study investigated post-operative complications and mortality after acute abdominal surgery [19]. They found that patients undergoing major emergency abdominal surgery had far more complications than patients undergoing minor emergency abdominal surgery. Age, ASA score, performance score and medical comorbidities were risk factors for 30-day mortality.

Our study had some limitations. Overall, 376 patients undergoing major emergency abdominal surgery did not have a preoperative NLR measured in the study period. This increased the risk of selection bias since the reason for missing NLR was unknown. NLR may change rapidly, so the timing of the preoperative NLR may potentially be important. In our study, the timing of preoperative NLR ranged 72-0 hours before surgery. Unfortunately, there are only few previous studies of NLR and major emergency abdominal surgery. Therefore, this study chose a crude and exploratory statistical method, including NLR as a continuous variable. A more comprehensive analysis with a larger dataset would be interesting in future studies. Our study is a retrospective observational study, which increases the risk of potential confounders.

We aimed to determine if preoperative NLR was associated with mortality and post-operative complications in patients undergoing major emergency abdominal surgery. In conclusion, we found that NLR was significantly higher among patients who died within 30 days of surgery, but the finding was not significant in an adjusted model.

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Accepted 7 July 2021

Conflicts of interest none. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

Cite this as Dan Med J 2021;68(9):A09200689

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