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Original Article

Prognostic Value of Nutritional Markers for Long-Term Mortality in Patients Undergoing Endovascular Aortic Repair

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Objective: The relationship between nutritional status and morbidity and death in a number of diseases and disorders has garnered considerable attension. In patients having endovascular aneurysm repair (EVAR) for abdominal aortic aneurysms (AAA), we assessed the prognostic value of nutritional markers of albumin (ALB), body mass index (BMI), and geriatric nutritional risk index (GNRI) for long-term mortality.

Materials and Methods: Retrospective data analysis was done on patients who had undergone elective EVAR for AAA more than 5 years earlier.

Results: A total of 176 patients underwent EVAR for AAA between March 2012 and April 2016. The optimal cutoff value of ALB, BMI, and GNRI for predicting long-term mortality was calculated as 3.75 g/dL (area under the curve [AUC] 0.64), 21.4 kg/m^2 (AUC 0.65), and 101.4 (AUC 0.70), respectively. Low ALB, low BMI, and low GNRI as well as age ≥75 years, chronic obstructive pulmonary disease, chronic kidney disease, and active cancer were independent risk factors for long-term mortality.

Conclusion: Malnutrition, which is measured by ALB, BMI, and GNRI, is an independent risk factor for long-term mortality in patients receiving EVAR for AAA. Of the nutritional markers, the GNRI can be the most reliable nutritional indicator to identify a potentially high-risk group of mortality after EVAR.

Keywords: endovascular aneurysm repair, albumin, body mass index, geriatric nutritional risk index, mortality

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Introduction

Since endovascular aneurysm repair (EVAR) was introduced to the world by Juan Carlos Parodi in 1991,[1] it has been widely accepted as a less invasive substitute for traditional open surgical repair. One of the most important paradigm shifts is the aggressive adoption of EVAR to high-risk patients. EVAR was linked to decreased postoperative mortality and morbidity than open repair, suggesting that it should be considered the treatment of choice in high-risk patients.[2]

However, the finding that all-cause mortality is greater in patients with high-risk than those without cannot be easily dismissed[3,4]; it is important to consider not only operative risk and aneurysm-related death but also life expectancy, when deciding the treatment of abdominal aortic aneurysm (AAA). Although cardiovascular, pulmonary, and renal diseases are the most common risk factors contributing to greater surgical risk, recent studies have reported that the decreased physiologic reserve, influenced by aging, malnutrition, sarcopenia, cognitive impairment, and so on, may be associated with a reduced ability to recover from surgical stresses, leading to morbidity and mortality after surgery.[5]

Nutritional status is reported to be a crucial prognostic factor in various diseases and disorders. A laboratory parameter of serum albumin (ALB) and an anthropometric index of body mass index (BMI) have been commonly used as nutritional markers. Prior research have shown that hypoalbuminemia and lower BMI were associated with higher morbidity and mortality in patients receiving EVAR.[6,7] Recently, the geriatric nutritional risk index

(GNRI), which is based on both ALB and BMI, has been proposed as an objective nutritional risk index by Bouillanne et al.[8] and has been shown to be a screening tool to assess nutrition-related morbidity and mortality after EVAR.[9,10]

To date, there have been no studies comparing ALB, BMI, and GNRI as prognostic factors for mortality following EVAR. In this study, we evaluated the prognostic value of nutritional markers of ALB, BMI, and GNRI for long-term mortality in patients undergoing EVAR for AAA.

Materials and Methods

Patients

Data on patients who had undergone elective EVAR for AAA over 5 years previously were obtained from a prospectively maintained database at the Department of Cardiovascular Surgery, Tokyo Medical University Hospital, and were retrospectively analyzed. The indication for EVAR comprised symptomatic AAA, asymptomatic AAA $\geq$5 cm in diameter, or rapidly expanding AAA (5 mm/6 months) according to the Guideline for the Diagnosis and Treatment of Aortic Aneurysm and Aortic Dissection issued by the Japanese Circulation Society (JCS).[11] Smaller AAA ($<$5 cm) in conjunction with common iliac artery aneurysm $\geq$3 cm in diameter or with the patient's strong wish for treatment was also included. Ruptured or mycotic AAA and isolated common or internal iliac artery aneurysms were excluded.

During the initial consultation, all the patients were asked whether they were willing to give written informed consent for their clinical data to be used for scientific presentations or publications. The procedures followed were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and the Helsinki Declaration of 1975, as revised in 2008. This study was approved by the clinical research committee of Tokyo Medical University, where it was conducted (TS2020-0388, January 15, 2021).

Baseline data on demographic and clinical characteristics, including age; sex; body weight and height; smoking history; concomitant diseases such as hypertension, dyslipidemia, diabetes mellitus, chronic obstructive pulmonary disease (COPD, defined as forced expiratory volume in 1 second $<$70%),[12] and chronic kidney disease (CKD, defined as estimated glomerular filtration rate $<$60 mL/s)[13]; history of cerebral vascular disease or ischemic heart disease; active cancer; and use of antiplatelet drugs, statins, or β-blockers, were retrieved from the database. Active cancer was defined as cancer detected within the preceding 6 months; recurrent, regionally advanced, or metastatic cancer; cancer for which any therapy had been administered within 6 months; or hematological cancer that was not in full remission.

Computed tomography (CT), with or without contrast medium, was carried out with 1.25-mm collimation. The dimensions of the proximal aortic neck, aneurysm sac, and distal iliac arteries was defined as the maximum minor axis diameter on an axial slice.[14] The minor axis was chosen to avoid overestimation of the size because of the tortuosity of the arteries. Patients who did not meet at least one of the aneurysm neck parameters were classified as being treated outside the instruction for use of each stent graft.

Nutritional assessment

The nutritional assessment included ALB (g/dL), BMI (kg/m^2), and GNRI. The GNRI was calculated using ALB and BMI recorded at admission, as previously described: $\text{GNRI} = 14.89 \times \text{ALB} + 41.7 \times \text{BMI}/22$.[8,15,16] The ideal body weight in the present study was defined as the value calculated from the ideal BMI of 22, because of its validity, instead of the value calculated with the Lorentz formula used in the original GNRI equation.[16]

Surgical techniques

As previously stated, all procedures were carried out under general or regional anesthesia by or under the supervision of certified cardiovascular surgeons (TN, MK, et al.) in an operating room with a portable imaging system.[17,18] Technical success was defined as a satisfactory stent graft insertion that included successful passage of the delivery system, correct deployment of the stent graft, complete withdrawal of the delivery system, freedom from open conversion, and absence of type I or III endoleak.

Mortality

Patients were monitored according to the institutional policy, as reported previously.[17,18] Patients were observed through the database until death or the end of the follow-up period in November 2021, whichever happened first. Postoperative results included any causes of death. The status of the patients was determined by follow-up visits and, if they could not visit an outpatient office at our university hospital, by letter or phone.

Statistics

Results are presented as the mean $\pm$ standard deviation. Statistics analysis was performed with PRISM 9 for MAC OS X (GraphPad Software, Inc., La Jolla, CA, USA) and Mac Toukeikaiseki Ver.3 (Esumi, Tokyo, Japan). For continuous data, the normality of the distribution was determined using D'Agostino and Pearson omnibus normality test. Intergroup comparisons were made using Student's t-test for normally distributed data and the Mann–Whitney

U test for other data. Categorical data were assessed using Fisher's exact probability test or Pearson χ^2 test. Univariate and multivariate Cox proportional hazard analyses were performed to evaluate the association between the outcome and baseline characteristics; variables of $p<0.05$ were added into a multivariate model. Receiver operating characteristic (ROC) curves were created to assess sensitivity, specificity, and area under the curve (AUC) of ALB, BMI, and GNRI in predicting overall mortality. The optimal cutoff value was determined using the maximum value of the Youden index. Survival curves were constructed using the Kaplan–Meier method; curves were compared using the log-rank test.

Results

Patient characteristics

A total of 176 patients underwent EVAR for infrarenal AAA between March 2012 and April 2016. The subjects included 148 men and 28 women with a mean age of 78.5 years (range, 51–89 years). **Table 1** summarizes the clinical characteristics and operative data of the patients. The majority of patients had several comorbidities. The median follow-up period was 4.73 (range 0.03–9.28) years. Eighteen patients (10.1%) were lost to follow-up. During the follow-up period, 61 patients died (aneurysm-related death, 2; cancer, 25; pulmonary disease, 14; cerebral disease, 5; renal disease, 5; cardiac disease, 5; thoracic aortic aneurysm rupture, 1; drowning, 1; unknown causes but not related to the aneurysm, 3).

Optimal cutoff values of ALB, BMI, and GNRI for long-term mortality

The average values of ALB, BMI, and GNRI were 3.53 ± 0.41 g/dL, 22.8 ± 3.3 kg/m^2, and 100.3 ± 9.7, respectively. Patients who survived had significantly higher ALB, BMI, and GNRI compared with those who died (3.88 ± 0.43 g/dL vs. 3.68 ± 0.44 g/dL, $p=0.002$; 23.3 ± 3.3 kg/m^2 vs. 21.7 ± 3.0 kg/m^2, $p=0.002$; 102.0 ± 9.0 vs. 95.9 ± 8.96, $p<0.001$, respectively).

According to the ROC curves, the optimal cutoff value of ALB, BMI, and GNRI for predicting long-term mortality was determined as 3.75 g/dL (AUC 0.64, sensitivity 53.3%, specificity 72.2%, $p=0.002$), 21.4 kg/m^2 (AUC 0.65, sensitivity 50.0%, specificity 74.8%, $p=0.001$), and 101.4 (AUC 0.70, sensitivity 79.0%, specificity 60.0%, $p<0.001$), respectively. The AUC showed that the GNRI had better discrimination for long-term mortality than its individual components such as ALB and BMI (**Figs. 1a–1c**). Low ALB, low BMI, and low GNRI were defined as ALB <3.75 g/dL, BMI <21.4 kg/m^2, and GNRI <101.4, respectively.

Table 1 Patient characteristics

	No. of patients (%)/ mean±SD/median (range)
Age, year	78.5 years (51–89 years)
Age ≥75 years	107 (60.8)
Female	28 (15.9)
Nutritional status	
ALB, g/dL	3.53±0.41
BMI, kg/m^2	22.8±3.3
GNRI	100.3±9.7
Smoking history	
Active	38 (21.6)
History	114 (64.8)
Comorbidities	
Hypertension	137 (77.8)
Dyslipidemia	79 (44.9)
Diabetes	38 (21.6)
COPD	48 (27.3)
CKD	81 (46.0)
Cerebrovascular disease	59 (33.5)
Ischemic heart disease	89 (50.6)
Active cancers	48 (27.3)
Medication	
Antiplatelet drugs	69 (39.2)
Statins	75 (42.6)
β-Blockers	64 (36.4)
Aneurysm diameter, mm	52.4±7.9
Small aneurysms, <55 mm	114 (64.8)
Outside of instruction for users	29 (16.5)
Operative data	
Type of stent graft	
ePTFE-based	124 (70.5)
Polyester-based	52 (29.5)
Technical success	175 (99.4)
Internal iliac artery embolization	19 (10.8)
Operative endoleak	
Type I	0 (0)
Type II	31 (17.6)
Type III	1 (0.5)
Secondary interventions	33 (18.8)
Median follow-up period, years	4.73 (0.03–9.28)

SD: standard deviation; ALB: serum albumin; BMI: body mass index; GNRI: geriatric nutritional risk index; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; ePTFE: expanded polytetrafluoroethylene

Univariate and multivariate Cox regression analyses for long-term mortality

We performed univariate and multivariate Cox regression analyses of low ALB, low BMI, and low GNRI as well as conventional risk factors for long-term mortality. On univariate analysis, age ≥75 years, COPD, CKD, active cancer, and polyester-based stent grafts were substantially linked with long-term mortality. Low ALB, low BMI, and

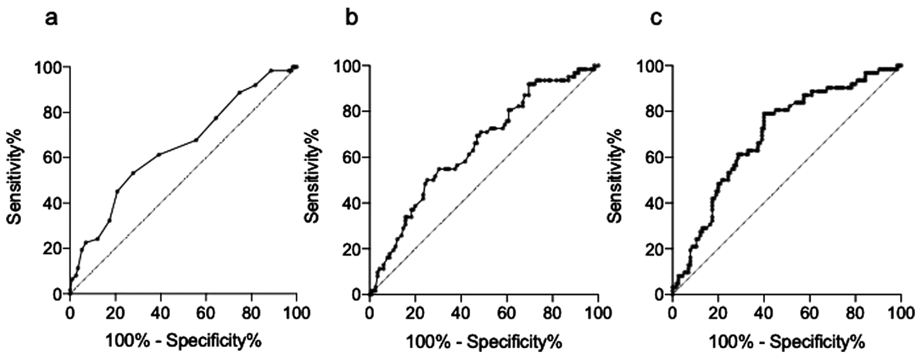


Fig. 1 Receiver operating characteristic curve for (**a**) albumin (ALB), (**b**) body mass index (BMI), and (**c**) geriatric nutritional risk index (GNRI). An area under the curve for ALB, BMI, and GNRI is 0.64, 0.65, and 0.70, respectively.

Table 2 Univariate and multivariate Cox regression analyses of risk factors for long-term mortality

	Univariate		Multivariate			
			Model 1		Model 2	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Age, ≥75 years	4.08 (2.12–7.84)	<0.001*	3.13 (1.60–6.11)	0.001*	3.47 (1.78–6.77)	<0.001*
Female	1.03 (0.95–1.11)	0.448				
Malnutrition						
ALB, <3.75 g/dL	2.24 (1.35–3.71)	0.002*	2.06 (1.20–3.52)	0.009*	—	—
BMI, <21.4 kg/m^2	2.89 (1.75–4.79)	<0.001*	2.40 (1.41–4.11)	0.009*	—	—
GNRI <101.4	4.49 (2.45–8.21)	<0.001*	—	—	4.98 (2.67–9.27)	<0.001*
Smoking						
Active	0.90 (0.49–1.67)	0.748				
History	0.81 (0.49–1.36)	0.431				
Comorbidity						
Hypertension	1.24 (0.66–2.33)	0.512				
Dyslipidemia	0.79 (0.47–1.32)	0.368				
Diabetes mellitus	1.08 (0.59–1.96)	0.799				
COPD	2.09 (1.25–3.50)	0.005*	1.83 (1.18–3.63)	0.001*	1.96 (1.16–3.30)	0.011*
CKD	1.81 (1.09–3.00)	0.023*	1.92 (1.11–3.29)	0.018*	1.81 (1.07–3.05)	0.027*
Cerebrovascular disease	1.35 (0.80–2.28)	0.255				
Coronary artery disease	1.11 (0.67–1.84)	0.676				
Active cancer	2.25 (1.35–3.76)	0.002*	2.38 (1.41–4.09)	0.001*	2.75 (1.61–4.64)	<0.001*
Medication						
Antiplatelet drugs	0.83 (0.49–1.39)	0.479				
Statin	0.79 (0.47–1.32)	0.369				
β-Blocker	0.92 (0.54–1.55)	0.746				
Aneurysm morphology						
Small aneurysm, <55 mm	0.70 (0.42–1.17)	0.177				
Outside of instruction for users	0.82 (0.39–1.74)	0.610				
Type of stent graft						
ePTFE-based	Reference		Reference		Reference	
Polyester-based	1.82 (1.09–3.06)	0.023*	1.32 (0.76–2.28)	0.321	1.17 (0.68–2.03)	0.571
Operative endoleak						
Type II	0.51 (0.24–1.06)	0.072				
Secondary interventions	0.75 (0.38–1.47)	0.397				

HR: hazard ratio; CI: confidential interval; ALB: serum albumin; BMI: body mass index; GNRI: geriatric nutritional risk index; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; ePTFE: expanded polytetrafluoroethylene; *Significant low GNRI were also significantly associated with long-term mortality (**Table 2**).

Based on the moderate to significant association between ALB or BMI and GNRI, multivariate analysis for overall mortality was carried out using two types of analyses: model 1 utilizing ALB and BMI as a covariant and model 2 using GNRI as a covariant. In model 1, age ≥75 years, ALB, BMI, COPD, CKD, and active cancer were detected as independent risk factors for long-term mortality. In model 2, age ≥75 years, GNRI, COPD, CKD, and active cancer were found to be independent risk factors for long-term mortality (**Table 2**).

Kaplan–Meier survival curves according to ALB, BMI, and GNRI

The Kaplan–Meier analysis demonstrated that the overall survival rate was significantly lower in patients with low ALB, low BMI, and low GNRI than those without (**Figs. 2a**–**2c**).

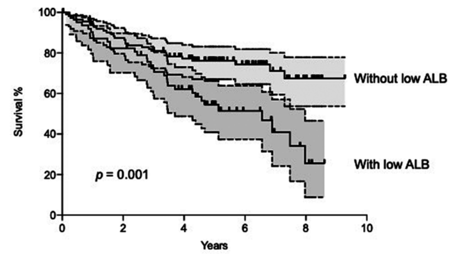
Discussion

In this work, we assessed the impact of malnutrition on long-term mortality following EVAR using the GNRI as a nutritional marker. Univariate and multivariate analyses detected low GNRI as an independent risk factor for predicting long-term mortality in patients undergoing EVAR. Similarly, as components of the GNRI, the results for ALB and BMI paralleled the GNRI. The ROC analysis demonstrated that the GNRI had a higher discriminating ability than ALB and BMI. These findings indicate that the GNRI may be the most accurate prognostic indicator for identifying a potentially high-risk group of mortality following EVAR.

The less invasive endovascular therapy, such as EVAR for AAA, is spreading rapidly, and the identification of being unfit for surgery has become an important issue.[5] Although cardiovascular, pulmonary, and renal disease are the most frequent risk factors contributing to greater surgical risk, recent research suggests that the decreased physiologic reserve, influenced by aging, malnutrition, sarcopenia, cognitive impairment, and other factors, may be linked to a decreased ability to recover from surgical stresses.[5]

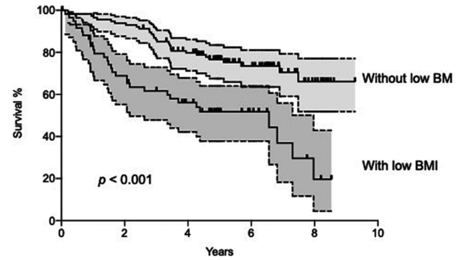
Malnutrition has two distinct clinical forms; one is protein deficiency and bilateral extremity swelling, while the other is weight loss and reduction in muscle mass and adipose tissue. ALB indicates the former type of malnutrition, and BMI is an index of the latter type of malnutrition; the GNRI, which is based on both ALB and BMI, can reflect both.[8] Accordingly, although ALB and BMI are still good predictors of morbidity and mortality, the GNRI has been shown to be a more reliable nutritional

a



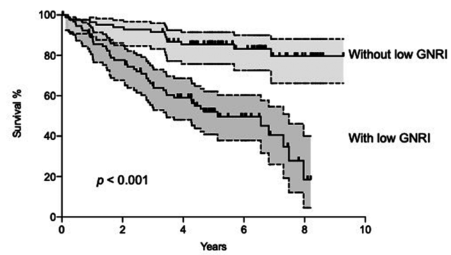
Patient	Year	0	1	2	3	4	5	6	8
Without low ALB	Survival, %	100	93.7	87.4	81.0	77.2	76.2	74.4	67.4
	SE, %	0.0	2.3	3.2	3.7	4.0	4.1	4.4	6.2
	At risk	103	104	97	90	80	53	39	11
With low ALB	Survival, %	100	92.2	79.7	64.1	60.9	54.5	52.2	22.8
	SE, %	0.0	3.8	4.9	5.7	6.2	5.4	6.9	10.3
	At risk	63	57	53	44	36	24	13	4

b



Patient	Year	0	1	2	3	4	5	6	8
Without low BMI	Survival, %	100	97.4	93.9	86.0	79.8	76.6	73.5	66.1
	SE, %	0.0	1.5	2.2	3.2	3.8	4.0	4.5	6.4
	At risk	116	113	109	99	88	60	41	12
With low BMI	Survival, %	100	83.0	68.9	61.7	56.1	51.8	51.8	19.7
	SE, %	0.0	4.9	6.1	6.4	6.6	6.8	6.8	10.6
	At risk	60	48	40	35	28	15	11	2

c



Patient	Year	0	1	2	3	4	5	6	8
Without low GNRI	Survival, %	100	96.4	94.0	91.6	85.4	85.4	83.2	79.6
	SE, %	0.0	2.0	2.6	3.1	3.9	3.9	4.4	5.5
	At risk	83	81	79	77	68	49	36	12
With low GNRI	Survival, %	100	89.0	77.7	65.1	59.2	52.1	49.6	18.6
	SE, %	0.0	3.3	4.4	5.1	5.3	5.5	5.8	9.7
	At risk	93	80	70	57	48	26	16	3

Fig. 2 (**a**) Kaplan–Meier survival analysis of long-term survival between patients with low albumin (ALB) and those without. Shaded region shows a 95% confidence interval (CI). Standard error (SE) <10% for estimates up to 8 years. (**b**) Kaplan–Meier survival analysis of long-term survival between patients with low body mass index (BMI) and those without. Shaded region indicates a 95%CI. SE <10% for estimates up to 8 years. (**c**) Kaplan–Meier survival analysis of long-term survival between patients with low geriatric nutritional risk index (GNRI) and those without. Shaded region shows a 95%CI. SE <10% for all estimates.

indicator of morbidity and mortality in various pathological conditions, including cancer, CKD, heart failure, cardiovascular disease, etc., than ALB or BMI alone.[19–22) In this study, multivariate analysis found low ALB, low BMI, and low GNRI as independent risk factors for predicting long-term mortality following EVAR, while the ROC analysis showed that the GNRI (AUC: 0.70) had a stronger discriminating ability than ALB (AUC: 0.64) and BMI (AUC: 0.65). The risk of mortality at low GNRI was also apparent by Kaplan–Meier survival curves.

The GNRI was defined as four grades of nutrition-related risk: major risk (GNRI: $<$82), moderate risk (GNRI: 82 to $<$92), low risk (GNRI: 92 to $\leq$98), and no risk (GNRI: $>$98) and suggested that the risk of death or infectious complications was significant in patients with major, moderate, or low nutrition-related risks than those with absent nutrition-related risk.[8] The cutoff value of the GNRI (101.4) determined in this study was close to the normal GNRI cutoff value of 98 as proposed by Bouillanne et al.,[8] suggesting that it should be noted that patients even with low nutrition-related risk may have a poor long-term prognosis after EVAR.

EVAR did not increase overall life expectancy in patients physically ineligible for open repair, although it could decrease aneurysm-related mortality.[23,24] Determining the life expectancy of patients is crucial to ensure that they receive appropriate care and support. However, the life expectancy is challenging to forecast, and no techniques for stratifying patient selection have been created. As seen in this study, patients undergoing EVAR often had serious malnutrition, which significantly decrease the physiologic reserve. We should be mindful of the effects of malnutrition and take into account preoperative evaluation and optimization of nutritional status in this high-risk population; we sometimes have to dare to observe the progress of the disease without surgery for these patients.

Study limitations

Our study has the following limitations. First, this was a retrospective study based on a prospective but single-center database, which had potentially limited external validity. Second, the series was relatively small but consecutive. Patient selection bias was minimized, and these results were comparable to previous reports. Third, the follow-up rate was slightly low because of the pandemic of COVID-19. Finally, one preoperative measurement of ALB, BMI, and GNRI did not necessarily represent a patient's state of nutrition; a change in a patient's condition may have occurred between nutrition assessment and operation or follow-up and may not have been detected.

Conclusion

Malnutrition, which is determined by ALB, BMI, and GNRI, is an independent risk factor of long-term mortality in patients after EVAR for AAA. The GNRI can be the most accurate nutritional indicator to spot a potentially high-risk group of mortality following EVAR. Vascular specialists should keep in mind the implications of malnutrition and consider the preoperative evaluation and optimization of nutritional status in this high-risk population.

Disclosure Statement

The authors report no actual or possible conflict of interest in relation to this article.

Author Contributions

Study conception: TN
Data collection: TN, MK, RM, HO
Analysis: TN, JK
Investigation: TN, MK
Manuscript preparation: TN, AD
Funding acquisition: N/A
Critical review and revision: all authors
Final approval of the article: all authors
Accountability for all aspects of the work: all authors

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