Malperfusion syndrome in patients undergoing repair for acute type A aortic dissection: Presentation, mortality, and utility of the Penn classification

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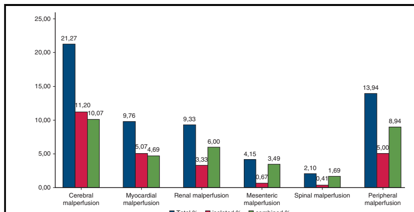
ABSTRACT

Background: The current study aims to report the presentation of the malperfusion syndrome in patients with acute type A aortic dissection admitted to surgery and its impact on mortality.

Methods: Data were retrieved from the multicenter European Registry of Type A Aortic Dissection. The Penn classification was used to categorize malperfusion syndromes. A machine-learning algorithm was applied to assess the multivariate interaction's importance regarding in-hospital mortality.

Results: A total of 3902 consecutive patients underwent repair for acute type A aortic dissection. Local malperfusion syndrome occurred in 1584 (40.59%) patients. Multiorgan involvement occurred in 582 patients (36.74%) whereas 1002 patients (63.26%) had single-organ malperfusion. The prevalence was the greatest for cerebral (21.27%) followed by peripheral (13.94%), myocardial (9.7%), renal (9.33%), mesenteric (4.15%), and spinal malperfusion (2.10%). Multiorgan involvement predominantly occurred in organs perfused by the downstream aorta. Malperfusion significantly increased the risk of mortality ($P < .001$; odds ratio, 1.94 ± 0.29). The Boruta machine-learning algorithm identified the Penn classification as significantly associated with in-hospital mortality ($P < .0001$, variable importance = 7.91); however, 8 other variables yielded greater prediction importance. According to the Penn classification, mortality rates were 12.38% for Penn A, 20.71% for Penn B, 28.90% for Penn C, and 31.84% for Penn BC, respectively.

Conclusions: Nearly one half of the examined cohort presented with signs of malperfusion syndrome predominantly attributable to local involvement. More than one third of patients with local malperfusion syndrome had a multivessel involvement. Furthermore, different levels of Penn classification can be used only as a first tool for preliminary stratification of early mortality risk. (J Thorac Cardiovasc Surg 2025;170:687-97)



Type of malperfusion	Total n.	%	Isolated	%	combined	%
Cerebral	830	21,27	437	11,2	393	10,07
Peripheral	544	13,94	195	5	349	8,94
Myocardial	381	9,76	198	5,07	183	4,69
Renal	364	9,33	130	3,33	234	6
Mesenteric	162	4,15	26	0,67	136	3,49
Spinal	82	2,1	16	0,41	66	1,69

Incidence of organ malperfusion.

CENTRAL MESSAGE

Nearly half of patients had signs of malperfusion. More than one third of patients had a multivessel involvement. The Penn classification can be used only as a first tool for prediction of mortality.

PERSPECTIVE

The current literature offers varying incidence rates and discrepant results correlating malperfusion to mortality. Our analysis provides some new insights into the incidence rates of malperfusion and the associated mortality after surgical repair of type A acute aortic dissection. The analysis is based on the data of 3902 consecutive patients from 18 European centers.

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Abbreviations and Acronyms

ERTAAD	= European Registry of Type A Aortic Dissection
IQR	= interquartile range
OR	= odds ratio

Surgical repair of acute type A aortic dissection is still associated with significant mortality rates. In this regard, large registries report mortality rates of approximately 18%.[1-3] As a result of the preoperative ischemic damages caused by the false lumen, organ and global malperfusion remains one of the strongest independent risk factors for in-hospital mortality and early complications.[4,5]

The current literature reports varying incidence rates and presents discrepant results when correlating malperfusion to mortality.[6-9] This discrepancy can be attributable to different definitions, complex nature, and plurality of the presentation.[10] In this setting, the University of Pennsylvania classification system (Penn class) has been introduced to categorize the severity and heterogeneity of malperfusion.[11] Moreover, this system has been demonstrated to provide better discrimination for early mortality compared with other classification systems.[12] Given the aforementioned discordances, the current study sought to explore malperfusion in its incidence and correlation to mortality in a large multicenter cohort of patients.

METHODS

Study Population and End Points

The analysis was determined on the basis of the data from 3902 consecutive patients from the European Registry of Type A Aortic Dissection (ERTAAD) registry. This was a multicenter, retrospective cohort including consecutive patients operated for acute type A aortic dissection at 18 centers of cardiac surgery located in 8 European countries (Belgium, Czech Republic, Finland, France, Germany, Italy, Spain, and the United Kingdom) from January 2005 to March 2021.

The institutional review board and ethics committee of the University Hospital Muenster (June 18, 2021, diary no. 2021-368-f-S) approved this retrospective study. According to the approval, individual informed consent was not required in this retrospective analysis and therefore waived. Moreover, the ERTAAD is registered in ClinicalTrials.gov with the identifier NCT04831073 (https://clinicaltrials.gov/study/NCT04831073).

Six different preoperative organ malperfusions were reported according to the study protocol.[13] Myocardial malperfusion was defined as any changes in ST level on electrocardiogram and/or an increase in cardiac enzymes; cerebral malperfusion as acute preoperative stroke; spinal malperfusion as acute paraparesis/paraplegia; mesenteric malperfusion as sudden, mild-to-severe abdominal pain with or without nausea and vomiting, accompanied or not by rectal bleeding or bloody diarrhea; renal malperfusion as anuria/oliguria; and peripheral malperfusion as loss of pulse with or without sensory or motor deficits of any limb.

Malperfusion was further categorized according to the Penn classification. Patients without malperfusion were classified as Penn A. In Penn B were included patients with the presence of isolated or multidistrict vessel involvement. In Penn C were patients with a global malperfusion and in Penn class BC there were patients in whom both conditions were present (local and global). The main end point of this study was in-hospital mortality focusing on the Penn classification. Single contributions of organ malperfusion with or without the presence of concomitant global malperfusion to the in-hospital mortality were analyzed in the second analysis. Finally, a third analysis was carried out with the end point being the long-term mortality of discharged patients with a focus on Penn classification.

Statistical Analysis

Continuous variables are presented as median and interquartile range (IQR) differences. Categorical variables are shown as counts and percentages. Differences across Penn groups were assessed using the Kruskal/Dunn or Fisher exact test for continuous or binary variables. Multivariate interaction variable importance for in-hospital mortality was performed using the Boruta machine-learning algorithm, as this method offers a better prediction in large datasets.[14,15]

Moreover, the use of machine-learning algorithms, which are ensembles of multivariate decision trees, was motivated by its ability to address the limitations inherent in multivariate binomial logistic regression, such as independence of observations, linearity of log-odds, absence of multicollinearity, and strong outliers in predictors. If any of these assumptions are not met in the data, the multivariate logistic model outputs (highly) biased odds ratios (ORs). In contrast, Boruta offers several advantages: it naturally handles multicollinearity through random subsets of predictors and mitigates the effects of outliers via the robust partitioning ability of decision

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trees. In addition, Boruta captures complex nonlinear and multivariate interactions between predictors and outcomes, which are essential for understanding risk in our dataset. Our main motivation for using Boruta is its ability to identify risk factors for in-hospital death (ie, feature selection) which, nonlinearly and in complex interactions lead to an increase in mortality.

ORs of isolated local malperfusions and interactions with the global malperfusion were obtained using bivariate bootstrapped logistic regressions with a total of 1000 samples. Survival estimates were generated for the long-term cohort using Kaplan-Meier analysis. Cox regression analysis including only discharged patients was performed to explore the behavior of Penn classes after discharge. Data analysis was performed using Excel 2016 (Microsoft) and R software, (RStudio 4.3.3).

RESULTS

Patients' Presentation and Incidence of Malperfusion

A total of 1648 patients (42.23%) presented with signs of preoperative malperfusion, whereas more than one half (2254 patients 57.77%) did not present with malperfusion (Penn A). Isolated organ malperfusion was present in 24.62% (961) of patients (Penn B), whereas 263 (6.74%) had a global malperfusion (Penn C). A combination of organ malperfusion and global malperfusion was found in 424 patients (10.86%) (Penn BC) (Figure 1 summarizes malperfusion according to the Penn classification.)

In total, 2363 organ malperfusions were diagnosed. The most frequent malperfusion was cerebral malperfusion (830 patients, 21.27%) followed by peripheral (544 patients, 13.94%), myocardial (381 patients, 9.7%), renal (364 patients, 9.33%), mesenteric (162 patients, 4.15%), and spinal malperfusion (82 patients, 2.10%). Involvement of more than 1 organ occurred in 582 patients (14.92%), whereas 1002 patients (25.69%) had single organ malperfusion. Involvement of more than one organ was more frequent in organs perfused by the distal descending aorta. Figure 2 displays the rates of organ malperfusions.

Preoperative data are summarized in Tables 1 and 2 details intraoperative data. Moreover, rates and combinations of organ malperfusions are presented in Table 3. Patients classified into group C were significantly older than those in the other 3 groups. Preoperative arterial lactate and creatinine values were significantly lower in patients without malperfusion and significantly increased progressively across the 3 Penn groups. The estimated distance to the hospital was similar across the groups; however, the time between the onset of the symptoms and the beginning of the operation was significantly longer in patients without malperfusion, indicating prioritization of the surgery for patients with malperfusion. The rates of preoperative cardiac massage, pericardial effusion, and intubation at the hospital admission were significantly greater in patients with malperfusion. Patients with local malperfusion (group B) had a significantly greater rate of tears in ascending aorta than patients without malperfusion.

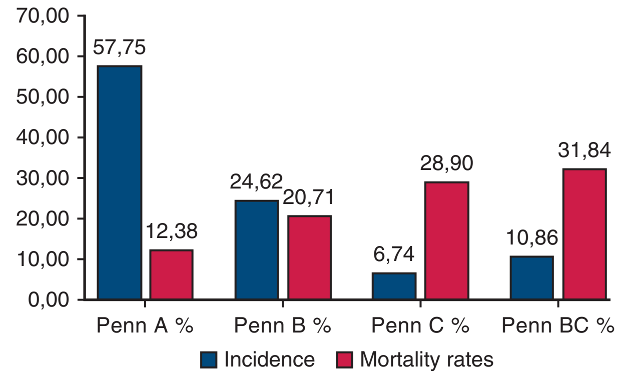


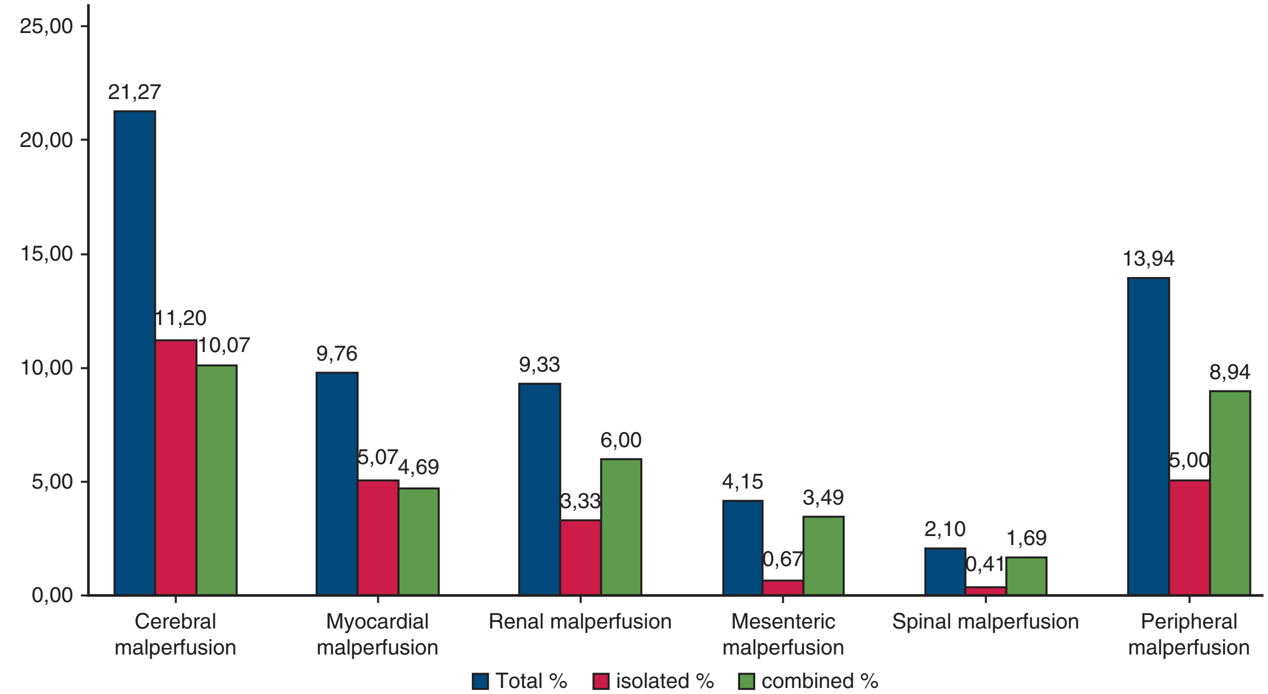
FIGURE 1. Incidence and mortality rates according of Penn classification.

The intraoperative rates of root replacement were significantly higher in Penn A than in Penn B, whereas the proportion of distal repair was relatively similar across groups.

Risk and Rates of Mortality

Patients without malperfusion (Penn A) reported a mortality rate of 12.38%, whereas patients with malperfusion showed mortality rates of 20.71% in Penn B, 28.90% in Penn C, and 31.84% in Penn BC, respectively (Figure 1). The Boruta machine-learning algorithm identified the Penn classification as significantly associated with in-hospital mortality ($P < .0001$, variable importance = 7.91, Table 4). Table 3 details the results of the machine-learning analysis. Bootstrap analysis revealed a roughly 2-fold probability of mortality after organ malperfusion ($P < .0001$; OR, 1.94, OR_IQR, 0.29). The presence of global malperfusion further increased the mortality risk ($P < .0001$; OR, 2.54, OR_IQR, 0.48). Spinal malperfusion was not significantly associated with increased mortality ($P = .23$), whereas all other organ malperfusions significantly heightened mortality to varying degrees. The lowest odds for mortality were determined by the renal malperfusion (OR, 1.65; OR_IQR, 1.65, $P = .047$) and this increased to 2.70 (OR, 2.7; OR_IQR, 1.16) if it was combined with the presence of a global malperfusion (Penn BC). The highest odds for in-hospital mortality were observed with mesenteric malperfusion (OR, 3.07; $P = .001$), without any interaction with global malperfusion. Myocardial malperfusion combined with circulatory collapse presented the highest odds for mortality (OR, 3.10; OR_IQR 0.56; $P < .001$). Figure 3 reports in detail the results of the bivariate bootstrapped logistic regressions.

Survival analysis of discharged patients revealed after a median follow-up of 3.7 (IQR, 0.46) years, survival of 83.7% and 66.1% for patients in Penn A, 80.8%, and 62.5% in Penn B, 77.1% and 58.6% in Penn C, and 73.9.2% and 52.1% for patients in Penn BC after 5 and 10 years,



Type of malperfusion	Total n.	%	Isolated	%	combined	%
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Mesenteric	162	4,15	26	0,67	136	3,49
Spinal	82	2,1	16	0,41	66	1,69

FIGURE 2. Incidence of organ malperfusion.

TABLE 1. Preoperative baseline characteristics of patients and their differences classified according to the Penn classification

Preoperative variables	Penn A	Penn B	Penn C	Penn BC	Penn A ~ Penn B	Penn A ~ Penn C	Penn A ~ Penn BC	Penn B ~ Penn C	Penn B ~ Penn BC	Penn C ~ Penn BC
Age	64.21 ± 19.28	63.2 ± 19.85	68.76 ± 19.01	65.56 ± 17.43	n.s.	0.001	n.s.	<0.001	0.047	0.047
Octogenarians	8.4% (190/2254)	6.6% (63/961)	13.7% (36/263)	8.5% (36/424)	n.s.	0.027	n.s.	0.002	n.s.	n.s.
Female	31.4% (708/2254)	27.6% (265/961)	32.7% (86/263)	29.7% (126/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Genetic syndromes	2.4% (54/2254)	1.6% (15/961)	1.1% (3/263)	2.1% (9/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Marfan syndrome	2.2% (49/2254)	1.5% (14/961)	0.8% (2/263)	1.9% (8/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Height	173 ± 15	175 ± 15	173 ± 13.25	175 ± 12.75	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Weight	80 ± 20	80 ± 20	80 ± 20	80 ± 19.5	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Diabetes	5.2% (117/2252)	4.6% (44/961)	4.9% (13/263)	5.2% (22/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Hypertension	72.4% (1631/2254)	69.6% (669/961)	68.1% (179/263)	72.4% (307/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Previous stroke	2.9% (66/2254)	5.3% (51/961)	2.3% (6/263)	7.1% (30/424)	0.005	n.s.	0.001	n.s.	n.s.	0.024
Pulmonary disease	8.6% (194/2254)	7.7% (74/961)	9.5% (25/263)	8% (34/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Extracardiac arteriopathy	4.1% (93/2254)	5.7% (55/961)	6.1% (16/263)	8.3% (35/424)	n.s.	n.s.	0.003	n.s.	n.s.	n.s.
Recent myocardial infarction	3% (67/2254)	3.2% (31/961)	5.7% (15/263)	6.6% (28/424)	n.s.	n.s.	0.003	n.s.	0.019	n.s.
Previous cardiac surgery	3.3% (75/2254)	3.4% (33/961)	3% (8/263)	1.4% (6/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Poor mobility	4.4% (99/2254)	3.5% (34/961)	3% (8/263)	4.2% (18/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
CKD classes	73.2 ± 31.78	65.96 ± 33.99	59.9 ± 33.33	60.01 ± 36.81	<0.001	<0.001	<0.001	0.002	<0.001	n.s.

(Continued)

TABLE 1. Continued

Preoperative variables	Penn A	Penn B	Penn C	Penn BC	Penn A ~ Penn B	Penn A ~ Penn C	Penn A ~ Penn BC	Penn B ~ Penn C	Penn B ~ Penn BC	Penn C ~ Penn BC
Arterial lactate	1.3 ± 1.2	1.8 ± 1.96	2.5 ± 3.2	2.6 ± 3.4	<0.001	<0.001	<0.001	<0.001	<0.001	n.s.
eGFR, CKD-EPI	73.2 ± 31.78	65.96 ± 33.99	59.9 ± 33.33	60.01 ± 36.81	<0.001	<0.001	<0.001	0.002	<0.001	n.s.
Creatinine	88 ± 34.68	96.8 ± 42.44	99.44 ± 40.9	101.48 ± 48.75	<0.001	<0.001	<0.001	n.s.	0.002	n.s.
Hemoglobin	130 ± 26	132 ± 23	129 ± 27	128 ± 27	0.007	n.s.	0.015	0.02	<0.001	n.s.
Platelet count	196 ± 92	189 ± 94	178 ± 91	197 ± 125.5	0.045	0.018	n.s.	n.s.	n.s.	0.045
Thrombocytopenia	3% (58/1943)	5.6% (50/893)	7.8% (17/217)	7.1% (27/380)	0.004	0.004	0.002	n.s.	n.s.	n.s.
P2Y12 inhibitors	6.5% (146/2254)	4.6% (44/961)	6.8% (18/263)	6.8% (25/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Aspirin	17.5% (395/2254)	19.7% (189/961)	18.3% (48/263)	23.3% (99/424)	n.s.	n.s.	0.021	n.s.	n.s.	n.s.
Paraplegia, paraparesis	0% (0/2254)	6.7% (64/961)	0% (0/263)	4.2% (18/424)	<0.001	n.s.	<0.001	<0.001	n.s.	0.001
Estimated distance to hospital	25 ± 53	30 ± 51	34 ± 64.3	29 ± 53.5	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Onset of symptoms to surgery, h	8 ± 14	7 ± 6.25	6 ± 5.25	6 ± 5	<0.001	<0.001	<0.001	0.021	0.003	n.s.
Intubated sedated at arrival	6.6% (149/2254)	10.2% (98/961)	31.2% (82/263)	35.6% (151/424)	0.003	<0.001	<0.001	<0.001	<0.001	n.s.
Pericardial effusion	27.6% (621/2254)	24.8% (238/961)	49% (129/263)	48.1% (204/424)	n.s.	<0.001	<0.001	<0.001	<0.001	n.s.
Preoperative cardiac massage	0% (0/2254)	0% (0/961)	31.9% (84/263)	22.4% (95/424)	n.s.	<0.001	<0.001	<0.001	<0.001	0.024
Cardiogenic shock requiring inotropes	0% (0/2254)	0% (0/961)	90.9% (239/263)	96.5% (409/424)	n.s.	<0.001	<0.001	<0.001	<0.001	0.012
Salvage procedure	0.1% (2/2254)	0.1% (1/961)	31.2% (82/263)	22.2% (94/424)	n.s.	<0.001	<0.001	<0.001	<0.001	0.029
Tear in ascending aorta	61.4% (1384/2254)	67.4% (648/961)	66.9% (176/263)	67.5% (286/424)	0.005	n.s.	n.s.	n.s.	n.s.	n.s.
Iatrogenic TAAD	3.1% (71/2254)	1.4% (13/961)	4.9% (13/263)	1.4% (6/424)	0.026	0.009	n.s.	n.s.	0.004	n.s.
Bicuspid aortic valve	4.3% (96/2254)	3.9% (37/961)	3.8% (10/263)	1.9% (8/423)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Number of dissected visceral vessels	0 ± 0	0 ± 1	0 ± 0	0 ± 1	<0.001	n.s.	<0.001	<0.001	n.s.	<0.001
Ascending aorta size	50 ± 10	49 ± 10.2	52 ± 11.7	50 ± 9	n.s.	0.001	n.s.	<0.001	n.s.	0.001
Aortic arch size	36 ± 8	36 ± 7.9	37.35 ± 9.7	35 ± 8.33	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Any previous intervention on the aorta	1.6% (37/2253)	1.8% (17/960)	2.3% (6/263)	1.9% (8/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Aortic valve stenosis of any severity	2.4% (53/2254)	3.2% (31/961)	1.9% (5/263)	2.8% (12/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Tear in aortic arch	15.7% (354/2254)	18.2% (175/961)	14.4% (38/263)	18.6% (79/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Tear in aortic root	18.5% (418/2254)	16.3% (157/961)	17.1% (45/263)	16.5% (70/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Tear in the aortic arch at surgery	15.5% (350/2254)	18.1% (174/961)	14.4% (38/263)	18.6% (79/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Data are reported as means and standard deviations (in parentheses) or counts and percentages (in parentheses). *n.s.*, Not significant; *CKD*, chronic kidney disease; *eGFR/CKD-EPI*, estimated glomerular filtration rate/chronic kidney disease epidemiology collaboration; *TAAD*, type A aortic dissection.

respectively. Cox regression analysis revealed that classes C ($P = .035$; hazard ratio, 1.34; confidence interval, 1.02-1.76) and BC ($P < .001$; hazard ratio, 1.47; confidence interval, 1.17-1.84) were associated with increased long-term mortality after discharge compared with classes A and B. There was no significant difference in long-term survival between Penn classes B and A. Survival of discharged patients stratified according to the Penn classification was presented in Figure 4.

DISCUSSION

In this study, we demonstrated that nearly one half of the patients admitted to surgery presented with signs of preoperative malperfusion, predominantly attributable to local involvement. Specifically, multivessel involvement was more common in organs supplied by the downstream aorta. For instance, cerebral and cardiac malperfusions were isolated in 11.20% and 5.07% of cases, respectively, and

TABLE 2. Intraoperative baseline characteristics of patients and their differences classified according to the Penn classification

Intraoperative variables	Penn A	Penn B	Penn C	Penn BC	Penn A ~ Penn B	Penn A ~ Penn C	Penn A ~ Penn BC	Penn B ~ Penn C	Penn B ~ Penn BC	Penn C ~ Penn BC
Left subclavian/ axillary artery cannulation	1.8% (40/2254)	3.2% (31/961)	1.5% (4/262)	1.9% (8/424)	0.039	n.s.	n.s.	n.s.	n.s.	n.s.
Subclavian/axillary artery cannulation	39% (879/2254)	46.9% (451/961)	32.1% (84/262)	43.6% (185/424)	<0.001	n.s.	n.s.	<0.001	n.s.	0.01
Right subclavian/ axillary artery cannulation	37.3% (841/2254)	44.1% (424/961)	30.9% (81/262)	41.7% (177/424)	0.001	n.s.	n.s.	0.001	n.s.	0.015
Common femoral artery cannulation	31.1% (700/2254)	30.7% (295/961)	44.3% (116/262)	35.1% (149/424)	n.s.	<0.001	n.s.	<0.001	n.s.	n.s.
Carotid artery cannulation	1% (23/2254)	0.8% (8/961)	0.8% (2/263)	0.9% (4/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Aortic root replacement	29.6% (667/2254)	25.2% (242/961)	31.2% (82/263)	25.2% (107/424)	0.036	n.s.	n.s.	n.s.	n.s.	n.s.
AV repair	1% (22/2254)	1.1% (11/961)	0.4% (1/263)	0.7% (3/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
AV replacement	5.7% (128/2254)	4.4% (42/961)	5.7% (15/263)	4.2% (18/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Bentall procedure	22.9% (517/2254)	21.1% (203/961)	26.2% (69/263)	21.2% (90/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
David procedure	4.5% (101/2254)	2.9% (28/961)	3% (8/263)	2.8% (12/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Total arch replacement	14.1% (317/2254)	15.8% (152/961)	11.4% (30/263)	16.7% (71/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Beveled hemiarch repair	43.1% (972/2254)	45.5% (437/961)	47.9% (126/263)	44.6% (189/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Supracoronary aortic replacement	70.4% (1587/2254)	74.8% (719/961)	68.8% (181/263)	74.8% (317/424)	0.036	n.s.	n.s.	n.s.	n.s.	n.s.
Partial root repair	6.7% (152/2254)	6.8% (65/961)	9.1% (24/263)	12% (51/424)	n.s.	n.s.	0.002	n.s.	0.006	n.s.
Total aortic arch repair	14.1% (317/2254)	15.8% (152/961)	11.4% (30/263)	16.7% (71/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Conventional elephant trunk	2% (46/2254)	3.4% (33/961)	2.3% (6/263)	4.5% (19/424)	n.s.	n.s.	0.018	n.s.	n.s.	n.s.
FET	6.8% (135/1978)	8% (65/808)	3.4% (8/234)	8.5% (30/354)	n.s.	n.s.	n.s.	0.041	n.s.	0.048
TEVAR during the index hospitalization	0.2% (4/2254)	0.5% (5/961)	0% (0/263)	0% (0/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
TEVAR completion	0.6% (13/2254)	1.2% (12/961)	0.4% (1/263)	0.5% (2/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
CABG	8.6% (194/2254)	8.1% (78/961)	14.8% (39/263)	9.7% (41/424)	n.s.	0.008	n.s.	0.007	n.s.	n.s.
Mitral valve repair	0.5% (11/2254)	0.3% (3/961)	0.4% (1/263)	0.5% (2/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Mitral valve replacement	0.3% (7/2254)	0% (0/961)	0.8% (2/263)	0.2% (1/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Myocardial ischemic time	107 ± 72	109 ± 73	107 ± 65.5	109 ± 66.5	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Antegrade cerebral perfusion	64.2% (1446/2254)	70% (673/961)	62% (163/263)	70.5% (299/424)	0.005	n.s.	0.039	0.042	n.s.	n.s.
Retrograde cerebral perfusion	8.2% (184/2254)	8.9% (86/961)	6.8% (18/263)	5.7% (24/424)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

n.s., Not significant; *AV*, aortic valve; *FET*, frozen elephant trunk; *TEVAR*, thoracic endovascular aortic repair; *CABG*, coronary artery bypass graft.

combined with other malperfusions in 10.07% and 4.65%. Conversely, spinal malperfusion presented as isolated in 0.43% of the cases and in combination in 1.67%, mesenteric malperfusions presented as isolated in 0.67% and in association with other malperfusions in 3.49%. Behind the crude rate description, these findings highlight the surgical implication that distal malperfusion can often co-occur with other distal malperfusions, urging surgeons to tailor their use of resources and surgical strategies accordingly.

Regarding the proximal operations, we found that patients without malperfusions had a significantly greater rate of root replacement (29.6%) than patients with local malperfusion (25.2%). This can be explained by the fact that surgeons were keen to adopt a less-demanding and time-consuming strategy in patients with malperfusion (such as cerebral, or peripheral) to minimize complications and possibly reduce ischemic time.

Our findings using the Penn classification were consistent with those of Patrick and colleagues,[12] where similar rates were observed across the first 3 Penn groups. The notable difference was the incidence of Penn class C, which was 14.3% in their study compared with 6.74% in ours.[12]

TABLE 3. Rates and combinations of organ malperfusions

		Type of malperfusion					
No. patients	**Percentage**	**Myocardial**	**Cerebral**	**Spinal**	**Renal**	**Mesenteric**	**Peripheral**
437	11.20%		☑				
198	5.07%	☑					
195	5.00%						☑
140	3.59%		☑				☑
130	3.33%				☑		
63	1.61%	☑	☑				
50	1.28%		☑		☑		
38	0.97%				☑		☑
27	0.69%				☑	☑	
26	0.67%					☑	
23	0.59%	☑					☑
20	0.51%	☑	☑				☑
19	0.49%			☑			☑
19	0.49%		☑		☑		☑
16	0.41%					☑	☑
16	0.41%				☑	☑	☑
16	0.41%			☑			
15	0.38%		☑	☑			
13	0.33%	☑			☑		
12	0.31%	☑	☑		☑		
11	0.28%		☑			☑	
10	0.26%		☑		☑	☑	
9	0.23%		☑			☑	☑
8	0.21%		☑		☑	☑	☑
7	0.18%	☑			☑		☑
7	0.18%	☑	☑		☑		☑
6	0.15%	☑				☑	
5	0.13%	☑			☑	☑	
5	0.13%	☑	☑		☑	☑	
4	0.10%			☑	☑		☑
4	0.10%		☑	☑			☑
4	0.10%	☑				☑	☑
4	0.10%	☑	☑			☑	
3	0.08%	☑	☑	☑			
2	0.05%			☑		☑	☑
2	0.05%		☑	☑		☑	
2	0.05%		☑	☑		☑	☑
2	0.05%		☑	☑	☑		
2	0.05%	☑		☑			
2	0.05%	☑		☑			☑
2	0.05%	☑		☑	☑	☑	☑
2	0.05%	☑	☑		☑	☑	☑
1	0.03%			☑	☑		
1	0.03%			☑	☑	☑	

(Continued)

TABLE 3. Continued

No. patients	Percentage	Type of malperfusion					
		Myocardial	Cerebral	Spinal	Renal	Mesenteric	Peripheral
1	0.03%			☑	☑	☑	☑
1	0.03%		☑	☑	☑		☑
1	0.03%		☑	☑	☑	☑	☑
1	0.03%	☑	☑			☑	☑
1	0.03%	☑	☑	☑	☑		
1	0.03%	☑	☑	☑	☑	☑	☑

This discrepancy can be due to the different sample sizes of both groups (1192 vs 3902 patients of the current study), different local referral policies, and the assignation of myocardial malperfusion that can indicate both local and general ischemia.

Despite the aforementioned differences in the mortality rates for the first 3 Penn groups, we found, in line with the study of Patrick and colleagues,[12] increasing in-hospital mortality across the 4 groups. This increasing mortality across classes led the authors to consider the Penn classification as an excellent mortality discriminator compared with other classification systems. The Boruta algorithm identified the Penn classification as significantly associated with in-hospital mortality ($P < .001$); however, 8 variables demonstrated greater importance, indicating that a broader range of factors could enhance mortality discrimination beyond the Penn classification alone.

TABLE 4. Results of the multivariate interaction variable importance for in-hospital mortality using the Boruta machine learning algorithm

Variables	Variable importance	*P* value
Cardiopulmonary bypass time	13.58	<.0001
Creatinine	11.74	<.0001
Estimated distance to hospital	11.34	<.0001
Intubated sedated at arrival	10.29	<.0001
Urgency of the procedure	9.72	<.0001
Salvage procedure	8.36	<.0001
Age	7.80	<.0001
Invasive mechanical ventilation	8.51	<.0001
Penn classification	**7.91**	**<.0001**
Preoperative cardiac massage	8.28	<.0001
Platelet count	6.10	<.0001
Myocardial malperfusion	6.59	<.0001
Circulatory collapse	5.61	<.0001
Height	6.07	<.0001
Hypothermic circulatory arrest duration	5.56	<.0001
CABG	4.57	.003
Any malperfusion	4.17	.009
Hemoglobin	4.13	.014
Mesenteric malperfusion	3.96	.023

Bold indicates the highlight the Penn classification among other variables. *CABG*, Coronary artery bypass graft.

Regarding the contribution of single organ malperfusions to mortality, we found similar findings for preoperative peripheral malperfusion and coronary malperfusion according to the 3 most prominent type A aortic dissection registries (German Registry for Acute Aortic Dissection Type A, International Registry of Acute Aortic Dissection, and Nordic Consortium for Acute Type A Aortic).[6-8]

Regarding cerebral malperfusion the study of Wolfe and colleagues[8] from the International Registry of Acute Aortic Dissection registry including 6437 patients showed that cerebral and renal malperfusion were not associated with increased early mortality.[8] This discrepancy could be attributed to their separate categorization of cerebral malperfusion and coma, and broader criteria for renal malperfusion on the basis of the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) classification.

Spinal and visceral malperfusion were both from the Nordic Consortium for Acute Type A Aortic registry not associated with greater in-hospital mortality, whereas in the analysis of the German Registry for Acute Aortic Dissection Type A registry, both malperfusions were.[6,7] In our study, spinal malperfusion was not associated with increased mortality whereas mesenteric malperfusion was. As demonstrated in the present report, both malperfusions were almost always combined with other organ malperfusions, and this frequent combination might have obscured the individual contributions to mortality, which we addressed by employing bivariate bootstrapping regression. Furthermore, we focused on the interaction of the single malperfusions with the global malperfusion (Penn BC) according to the Penn classification to give a simpler

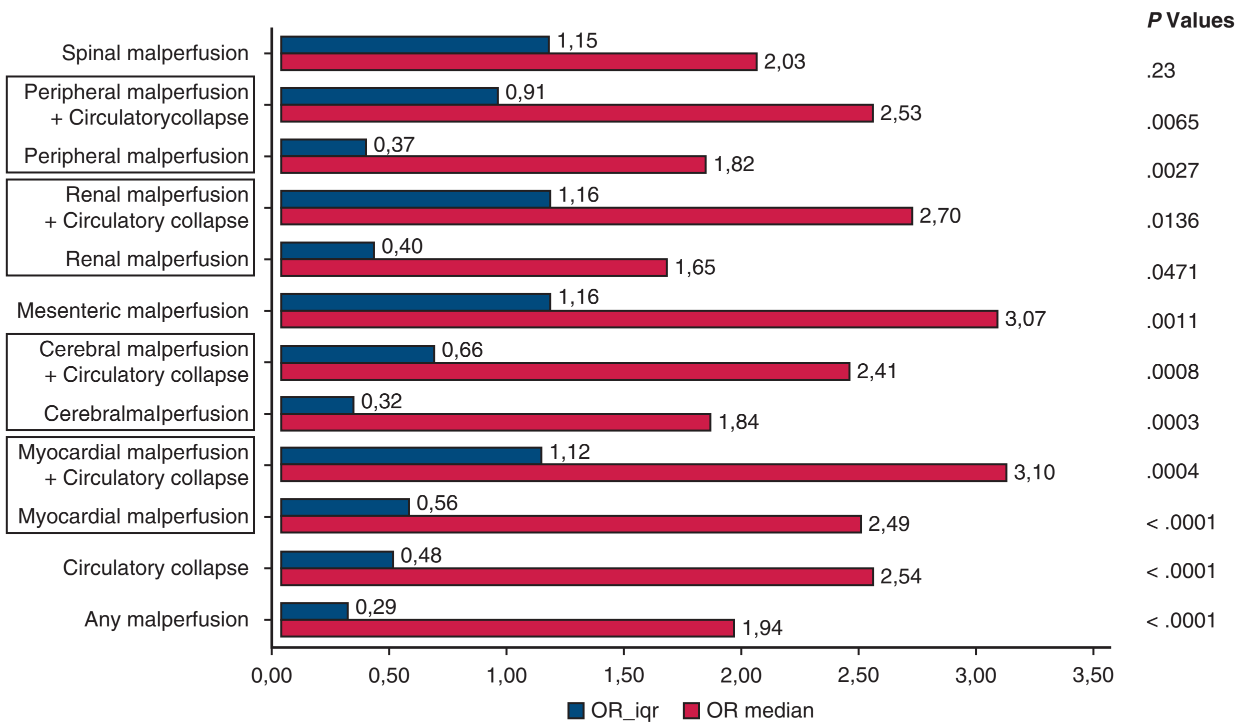

FIGURE 3. Odd ratios (ORs) obtained using bivariate bootstrapped logistic regressions. The *black boxes* indicate the interactions between single-organ malperfusion and circulatory collapse, causing an increment of odd ratio for mortality. *iqr*, Interquartile range.

estimation of the preoperative risk according to the study of Patrick and colleagues.[12]

Interestingly, discharged patients without organ malperfusion (Penn A) and those with it (Penn B) had similar survival probabilities, despite the greater in-hospital mortality among the latter (11.69% vs 21.04%). This discrepancy did not significantly affect postdischarge survival.

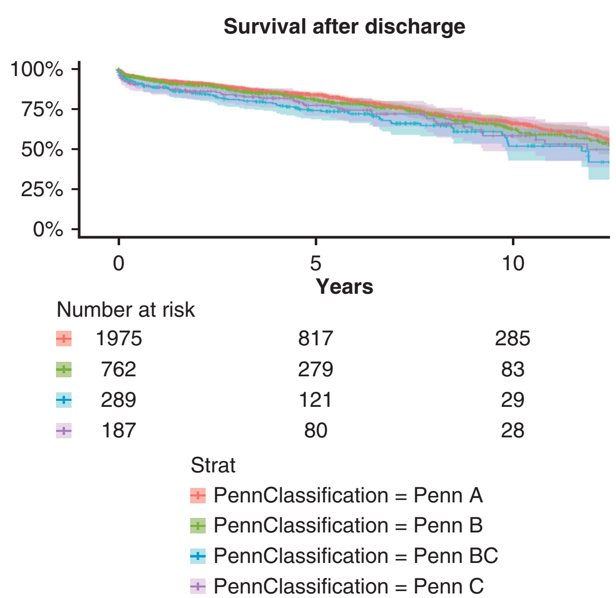

FIGURE 4. Survival of discharged patients stratified according to the Penn classification.

In our cohort completion of descending aortic treatment through thoracic endovascular aortic repair was greater in patients with Penn B compared with Penn A patients but not significant (0.6% Penn A vs 1.2% Penn B). In this regard, a direct correlation between survival and treatment attributable to the heterogeneity of presentations might be too complex for straightforward statistical analysis.

The present study has some limitations. The first one resides in the retrospective nature of the ERTAAD Registry. In this setting despite unique definitions of malperfusion valid for all centers,[13] slight differences in reporting the malperfusion rates cannot be excluded. Moreover, the present registry reports only patients who underwent surgical repair for acute type A aortic dissection. Therefore, the calculation of malperfusion incidences did not include patients not admitted to surgery.

In conclusion, this study revealed that nearly one half of our patient cohort presented with malperfusion syndromes, mainly as the result of local involvement. Distal malperfusions were often associated with multivessel involvement. Although the Penn classification provides a basic framework for mortality risk stratification, incorporating additional variables could yield a more precise prediction of in-hospital mortality, as suggested by machine learning analysis. Spinal malperfusion did not significantly impact

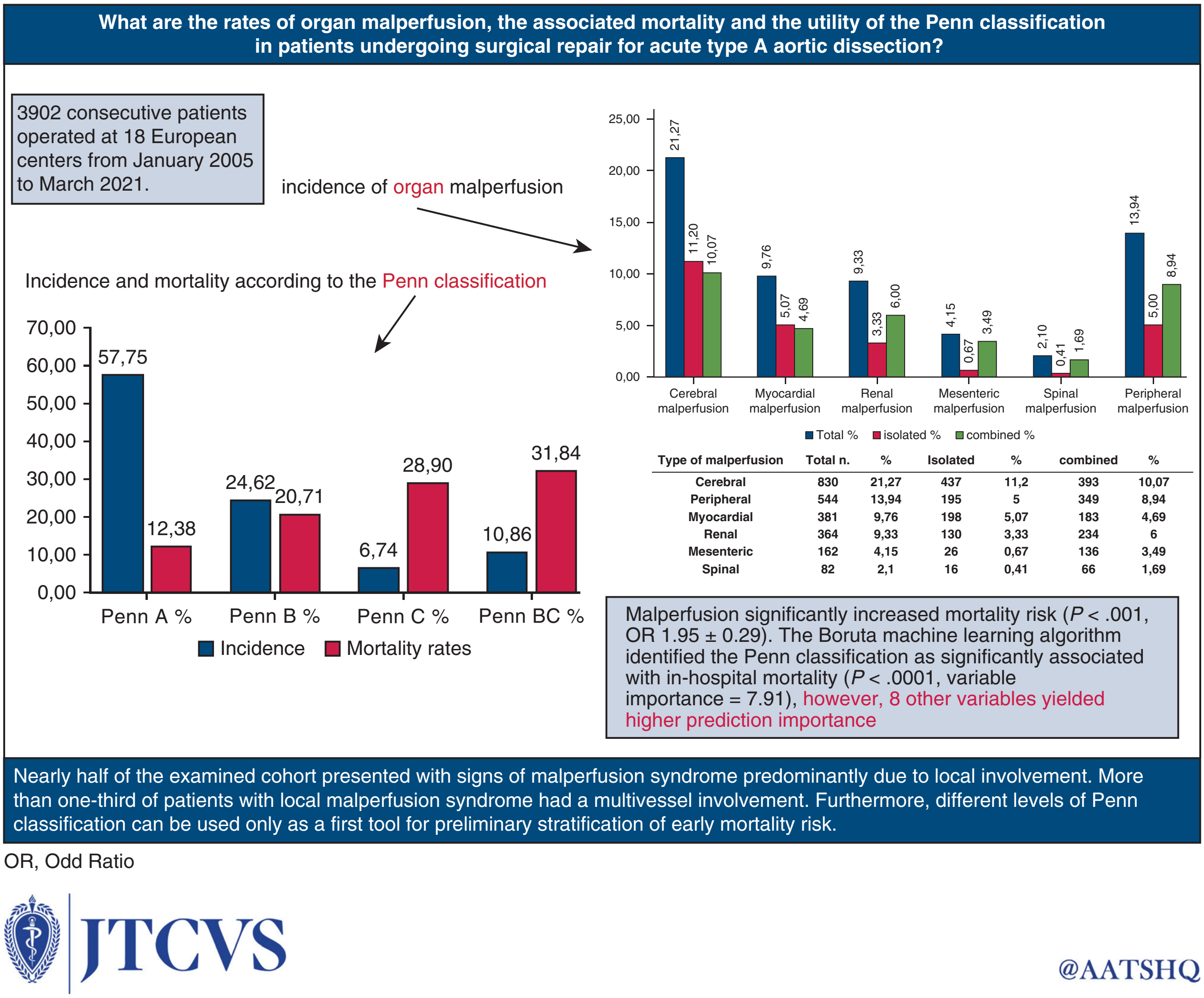

FIGURE 5. A total of 2363 organ malperfusions were diagnosed. Involvement of more than one organ was more frequent in organs perfused by the distal descending aorta. *OR*, Odds ratio.

in-hospital mortality, in contrast to other malperfusions, which were strong predictors of mortality. Moreover, the presence of preoperative organ malperfusion did not significantly reduce post-discharge survival compared to patients without malperfusion. See Figure 5 for a graphical abstract summarizing the study.

Conflict of Interest Statement

E.Q. receives payment or honoraria from Cardiva SL, AtriCure, Medtronic, and Edwards. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: aortic dissection, malperfusion, machine learning