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General Review

Risk Factors for Delirium after Vascular Surgery: A Systematic Review and Meta-Analysis

Linda Visser,[1] Anna Prent,[1] Louise B.D. Banning,[1] Barbara L. van Leeuwen,[2] Clark J. Zeebregts,[1] and Robert A. Pol[3]

Abstract: Background: Vascular surgery is considered a risk factor for the development of postoperative delirium (POD). In this systematic review we provide a report on the incidence and risk-factors of POD after vascular surgery.

Methods: A systematic literature search was conducted using Pubmed with the MeSH terms and key words "delirium" or "confusion", "vascular surgery procedures" and "risk factors or "risk assessment". Studies were selected for review after meeting the following inclusion criteria: vascular surgery, POD diagnosed using validated screening tools, and DSM-derived criteria to assess delirium. A meta-analysis was performed for each endpoint if at least two studies could be combined.

Results: Sixteen articles met the abovementioned criteria. The incidence of delirium ranged from 5% to 39%. Various preoperative risk factors were identified that is, age (Random MD 3.96, CI 2.57–5.35), hypertension (Fixed OR 1.30, CI 1.05–1.59), diabetes mellitus (Random OR 2.15, CI 1.30–3.56), hearing impairment (Fixed OR 1.89, CI 1.28–2.81), history of cerebrovascular incident or transient ischemic attack (Fixed OR 2.20, CI 1.68–2.88), renal failure (Fixed OR 1.61, CI 1.19–2.17), and pre-operative low haemoglobin level (fixed MD -0.76, CI -1.04 to -0.47). Intra-operative risk factors were duration of surgery (Random MD 15.68; CI 2.79–28.57), open aneurysm repair (Fixed OR 4.99, CI 3.10–8.03), aortic cross clamping time (fixed MD 7.99, CI 2.56–13.42), amputation surgery (random OR 3.77, CI 2.13–6.67), emergency surgery (Fixed OR 4.84, CI 2.81–8.32) and total blood loss (Random MD 496.5, CI 84.51–908.44) and need for blood transfusion (Random OR 3.72, CI 1.57–8.80). Regional anesthesia on the other hand, had a protective effect. Delirium was associated with longer ICU and hospital length of stay, and more frequent discharge to a care facility.

Conclusions: POD after vascular surgery is a frequent complication and effect-size pooling supports the concept that delirium is a heterogeneous disorder. The risk factors identified can be used to either design a validated risk factor model or individual preventive strategies for high-risk patients.

BACKGROUND

Postoperative delirium (POD) is a serious complication that occurs frequently among hospitalized elderly patients, with reported

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incidences up to 73.5%.[1] According to the Diagnostic and Statistical Manual of Mental Disorders (DSM) V criteria, POD is a syndrome characterized by disturbance in attention and awareness and additional disturbance in cognition, which develops over a short period of time.[2] Short-term complications include longer hospital length of stay, increased post discharge institutionalization and 30-day mortality.[1–4] Even on the long-term, POD is associated with persistent functional decline and increased mortality.[5] As a consequence of its heterogeneous nature, and because of fluctuating symptoms, POD is frequently unrecognized in the early stage.[3] Pre-operative geriatric consultation, but also prophylactic medical treatment may decrease the severity and duration of POD in high-risk patients.[6] Therefore, pre-operative risk assessment, which may indicate which patients are prone for POD, is very important, especially in elderly patients. Developments in operative and anesthetic techniques have led to a growing population of frail elderly patients considered to be suitable for major (vascular) surgery. In addition, several studies focusing on POD have identified that vascular surgery should be considered a risk factor for its occurrence.[4,7] As a result, a group of patients emerges that is exposed to a complication whose etiology is still not clear but can lead to unnecessary costs and mortality.

With this study we provide a systematic review of the available literature and provide a meta-analysis of the available data on predisposing and precipitating risk factors for the development of POD after vascular surgery.

MATERIAL AND METHODS

Literature Search

Reporting of this review was performed according to the PRISMA guidelines.[8] A literature search was performed until June 2020 using the Pubmed database. Over the last decade, multiple assessment tools have been created and validated, including the Confusion Assessment Method (CAM), the Neelon/Champagne Confusion Scale (NEECHAM) and the Delirium Observation Screening scale. Since the CAM was the first validated assessment tool and introduced in 1990, we only included studies from the period of January 1990 through June 2020. Search algorithms combined the medical subject heading (MeSH) terms and key words "delirium" or "confusion", "vascular surgery procedures", and "risk factors or "risk assessment". The search strategy was developed in conjunction with a medical librarian. Cross-referencing and the 'related-article' algorithm were used to identify additional articles. No search for unpublished data or abstracts was performed, nor did we contact leading authors in the field to retrieve unknown or new data.

Study Selection

Two authors (A.P. and L.V.) assessed the suitability of the identified studies. All studies reporting incidences and risk factors for POD in vascular surgery were considered for inclusion. Papers were included if they reported on original data on pre- intra- or postoperative risk factors, included only patients who underwent vascular surgery, had a control group of non-delirious patients, and provided data on delirium incidence. Duplicate publications, studies by the same authors with similar numbers of patients and comparable results, were excluded from the analysis. In some studies, there was a huge overlap in included patients. In that case, we included the study with the highest number of patients, which was usually the most recent publication. The study was registered in the PROSPERO database (registration number CRD42020210859).

Methodological Quality Assessment

For each of the selected studies, information was collected on the type of study, age, number and incidence of POD cases, type(s) of surgical procedure, method for diagnosing POD, sample size, and specific data on any pre-, intra- and postoperative risk factors. Because delirium is a complex of symptoms, all risk factors were potentially eligible for inclusion, although not all were necessarily included in pooled analyses. Two authors (A.P. and L.V.) independently assessed the methodological quality of the included studies. Quality assessment and risk of bias was assessed using the validated Quality in Prognostic Studies (QUIPS) tool. Risk of bias was ranked high, moderate or low in six domains. All studies were ranked independently by both the authors and in case of disagreement, the article was discussed in detail and consensus was reached.

Analysis

No assumptions were made with respect to potential risk factors prior to the literature search. A meta-analysis was performed for each endpoint if at least two studies could be combined. For dichotomous data the odds ratio (OR) was calculated with 95%

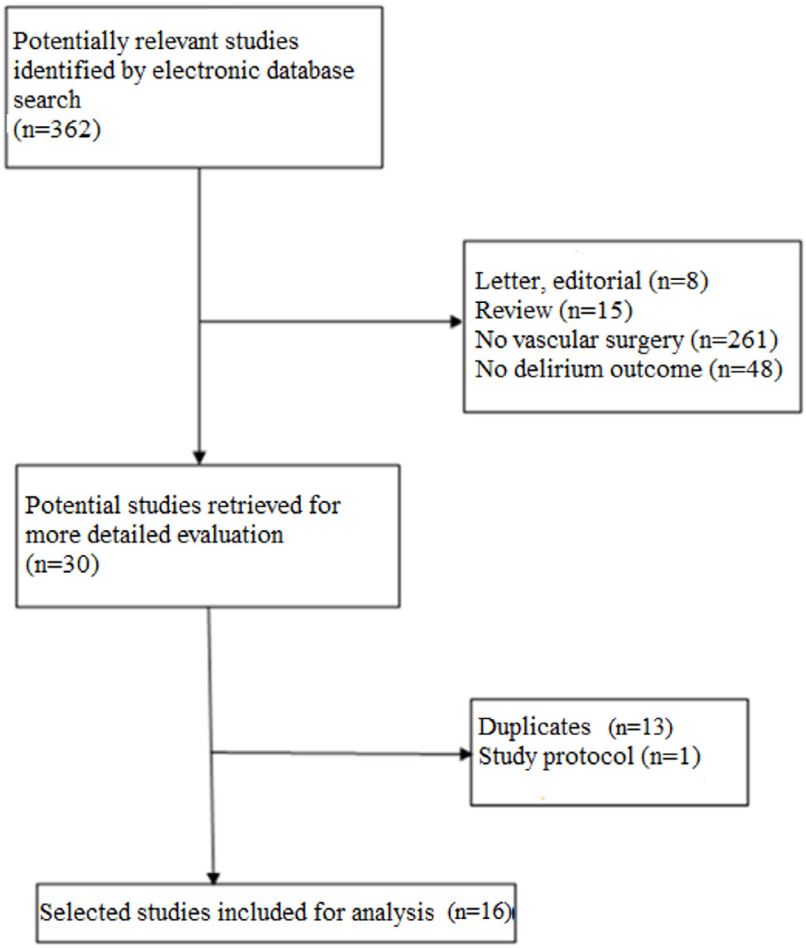

Fig. 1. Flow chart of identification of studies included in the meta-analysis.

confidence intervals (CI). For continuous data we calculated the mean difference (MD) with 95% CI. When the median and range were stated in the original papers, we used the methods of Luo and Wan to calculate the mean and standard deviation.[9,10]

Heterogeneity among studies was tested by Higgins I^2 statistic and Cochran Q-test with a significant level of $P = 0.1$. An $I^2 < 25\%$ indicated no heterogeneity, 25-50% moderate and >50% a high chance of heterogeneity.

In case of statistical heterogeneity (i.e., I^2 >50%) we used a random effect model; in other cases, a fixed model was used. All analyses were performed using Review Manager (RevMan, Version 5.0. The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen 2008).

After the initial search, 362 publications were considered potentially relevant and manually screened on the outcome POD, vascular surgery, incidence and risk factors (Fig. 1). Thirty publications met the inclusion criteria based on the abstract and were retrieved for full-text review. After further analysis, an additional 14 publications (one study protocol and 13 duplicate studies) were considered unsuitable. After excluding these publications,16 papers with a total of 4372 patients were included in the meta-analysis.[11–26] (Table I). Six studies used the DSM criteria, using various screening tools.[12,14,16,19,21,26] One study used the delirium rating scale,[12] three studies used the delirium observation screening tool[16,19,26] and one study used the delirium index.[14] The CAM method was used in seven studies to confirm the diagnosis of POD.[13,17,18,20,23–25] One study used the NEECHAM to Diagnose POD[15] and one study used the intensive care delirium screening checklist.[22]

In one retrospective study, it was not possible to diagnose POD by the DSM, CAM or NEECHAM, and therefore they used the transient advanced mental impairment.[11] (Table I)

The quality of the studies, based on the QUIPS method, is stated in Supplemental Table 2.

Table I. Characteristics of included studies on incidence of delirium in vascular surgery patients.

Study	Design	Country	Sample size	Age	Type of surgery	Elective/ emergency	POD Assessment	POD incidence
Rosen 2002	Retrospective	USA	188	>65	(Thoraca)abdominal aorta (open)	Elective	TAMI	28
Böhner 2003	Prospective	Germany	53	All	(Thoraca)abdominal aorta (open) carotid, peripheral bypass	Elective	DSM-IV	39
Minden 2005	Prospective	USA	35	All	Abdominal aorta (open)	Elective	CAM	23
Benoit 2005	Prospective	Canada	102	All	Abdominal aorta (open and EVAR)	Elective	DSM-IV	33
Katznelson 2009	Retrospective	Canada	582	All	Abdominal aorta (open and EVAR), peripheral bypass, amputation	Elective/ Emergency	NEECHAM	22
Koebrugge 2010	Prospective	The Netherlands	107	All	Abdominal aorta (open and EVAR)	Elective/ Emergency	DSM-IV	23
Bryson 2011	Prospective	Canada	88	>60	Abdominal aorta (open)	Elective	CAM	36
Sasajima 2012	Prospective	Japan	299	>60	Peripheral bypass, PTA	Elective	CAM	29
Visser 2015	Prospective	The Netherlands	566	>60	Abdominal aorta (open and EVAR), carotid, peripheral bypass, amputation, AV shunt, PTA	Elective	DSM-IV	5
Simoes 2015	Prospective	Protugal	56	All	Abdominal aorta (open), carotid, peripheral bypass	Elective	CAM	13
Sugimoto 2015	Retrospective	Japan	397	All	Abdominal aorta (open)	Elective	DSM-IV	12
Kawatani 2015	Retrospective	Japan	81	All	Abdominal aorta (EVAR)	Elective	ICDSC	25
Shin 2018	Retrospective	Korea	121	>60	Amputation	Elective	CAM	40
Styra 2018	Retrospective	Canada	173	All	Abdominal aorta (open and EVAR), carotid, peripheral bypass	Elecive	CAM	12
Lee 2018	Retrospective	Korea	1132	All	Abdominal aorta (open and EVAR), carotid, peripheral bypass, amputation	Elective	CAM	11.5
Roijers 2020	Retrospective	The netherlands	392	>65	Abdominal aorta, peripheral bypass, amputation, PTA	Elective	DSM-V	17.9

POD, postoperative delirium; TAMI, transent advanced mental imapairment; DSM, diagnostic and statistical manuel of mental disorders; CAM, confusion assessment method; NEECHAM, neelon/champagne confusion scale; ICDSC, intensive care delirium checklist.

Table II. Risk of bias.

Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and presentation	Overall
Rosen 2002		Low	Low	High		Moderate	Moderate
	Moderate				Moderate		
Böhner 2003		Low	Moderate	Low	Low	Low	Low
	Moderate						
Mindern 2005		Low	Low	Low	High	High	Moderate
	Moderate						
Benoit 2005		Low	Low	Low		Low	Low
	Moderate				Moderate		
Katznelson 2009	Low	Low	Low	Low		Low	Low
					Moderate		
Koebrugge 2010	Low	Low	Low	Low		Low	Low
					Moderate		
Bryson 2011	High		Low	Low	High	Moderate	Moderate
		Moderate					
Sasajima 2012		Low	Low	Low		Low	Low
	Moderate				Moderate		
Visser 2015	Low	Low	Low	Low	Low	Low	Low
Simoes 2015	High	Low	Moderate	Low	High	High	Moderate
Sugimoto 2015	Low	Low	Moderate	High	Low	Low	Moderate
Kawatani 2015	High	Low	Moderate	Low	Low	Low	Moderate
Shin 2018		Low	Low	Low	Low	Low	Low
	Moderate						
Styra 2018	Low	Low	Moderate	Low	Low	Low	Low
Lee 2018		Low	Moderate		Low	Moderate	Moderate
	Moderate			Moderate			
Roijers 2020	Low	Low	Low	Low	Low	Low	Low

Incidence and Risk Factors

The incidence of POD across studies ranged from 5% to 39% (Table I). The highest incidences were seen after amputation (range 17–63%),[15,19,24,26] and open aortic surgery (range 14–34%).[14–16,19,24] In all studies patients were followed for the first seven postoperative days or until discharge, and while results from individual studies varied, POD developed most often between the first and third postoperative day.[12,14,17,18,20,21] Thirteen studies reviewed individual risk factors. The risk factors found by each study are stated in Supplemental Table 1. We identified 13 risk factors that proved to be significant ($P< 0.05$) in univariate analysis which we will discuss in more detail below. Table II.

Predisposing Risk Factors

Age

The mean age ranged from 66 to 79 years. Age was assessed as a risk factor in 13 studies, which was reported as continuous variable in 12 studies and therefore suitable for meta-analysis.[12,14–16,18,24,26] Increasing age proved to be a significant risk factor for the occurrence of POD in the final analysis (Random MD 3.96, 95% CI 2.57–5.35 $n = 2342$, $P< 0.001$). (Table III)

Medical comorbidity

Eight studies examined the relationship between hypertension and POD.[11,15,18,19,21-23,26] There was no clear definition of hypertension, nor was there information about the pre- and intra-operative blood pressure or treatment. The incidence of POD was significantly higher in patients with hypertension compared to patients without hypertension: 26.8% vs. 21.8%, respectively (Fixed OR 1.30, 95% CI 1.05–1.59, $n = 2595$, $P= 0.01$). (Fig. 2A)

Diabetes mellitus (DM) was studied in nine studies.[11,15,18,19,20,21-23,26] In the meta-analysis, DM was associated with the development of POD. (Random OR 2.15, 95% CI 1.30–3.56, $n = 2664$) (Fig. 2B)

Hearing impairment was assessed in 4 studies.[11,12,23,26] The incidence of POD was 32.3% among the group with hearing impairment and 25.3% in the group without hearing impairment

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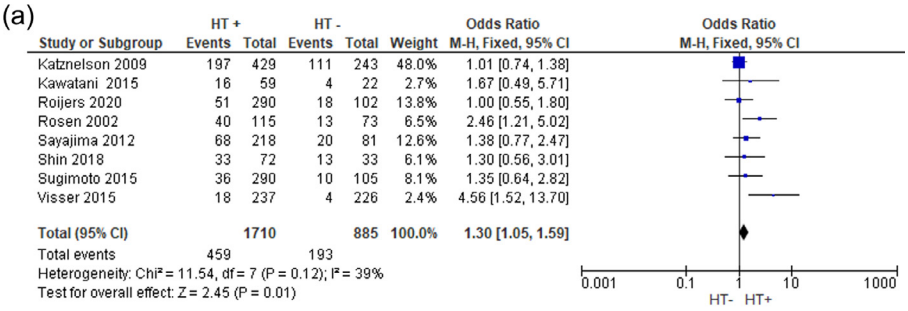

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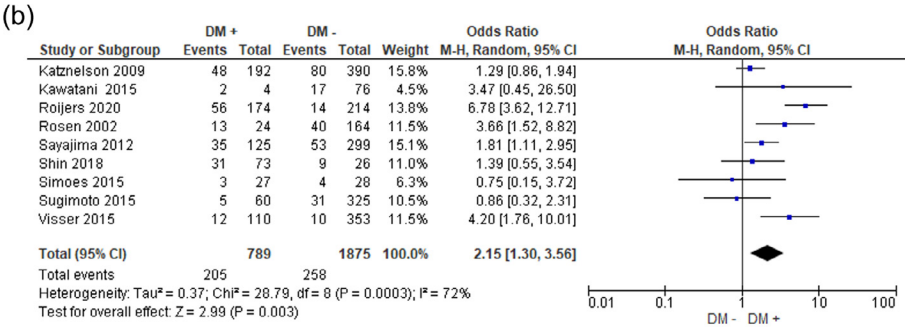

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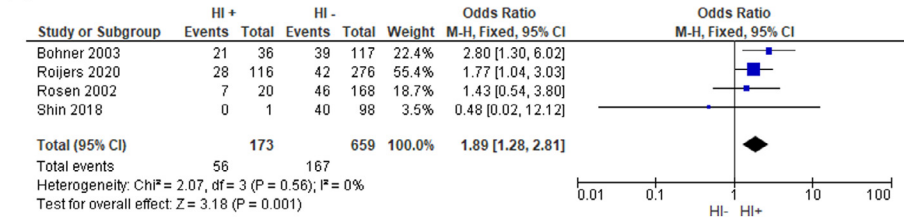

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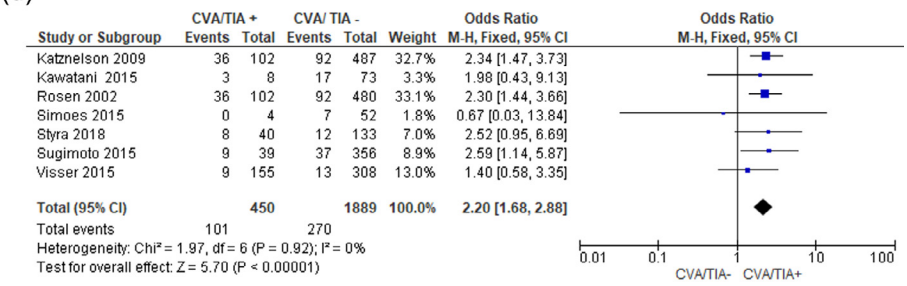

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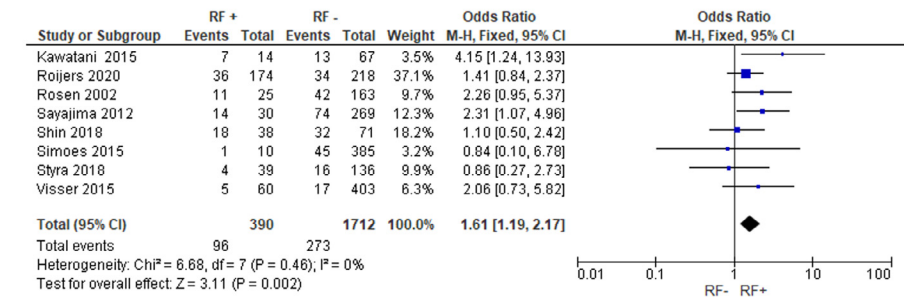


Fig. 2. (A) The association between hypertension (HT) and delirium. (B) The association between diabetes mellitus (DM) and delirium. (C) The association between hearing impairment (HI) and delirium. (D) The association between history of CVA or TIA and delirium. (E) The association between renal failure (RF) and delirium.

Table III. The association between age and delirium.

Study	Delirium present			Delirium absent			Weight (%)	Mean difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Böhner 2003	68.3	8.5	60	63.7	10.3	93	8.8	4.60 (1.60–7.60)
Benoit 2005	72.8	8.6	34	69.7	7.8	68	7.8	3.10 (-0.33–6.53)
Katznelson 2009	71.4	10.7	128	66.9	13	454	10.8	4.50 (2.29–6.71)
Koebrugge 2010	73.4	6.4	25	67.8	9.7	82	8.1	5.60 (2.33–8.87)
Sasajima 2012	75.0	10.0	88	70.0	11.0	211	9.9	5.00 (2.44–7.56)
Visser 2015	71.8	13.5	22	71.6	8.2	441	4.3	0.20 (-5.49–5.89)
Simões 2015	63	9	7	66	9	49	3.0	-3.00 (-10.13–4.13)
Sugimoto 2015	77/8	5.7	79	70.6	6.7	349	12.8	7.20 (5.76–8.64)
Kawatani 2015	78.7	7.5	20	73	7.6	61	7.0	5.70 (5.76–8.64)
Shin 2018	73.6	7	40	73.3	8	59	8.8	0.30 (-2.68–3.28)
Styra 2018	71.9	8.2	20	69.7	11.3	153	6.6	2.20 (-1.82–6.22)
Roijers 2020	80.1	6.8	70	76.2	5.2	322	12.1	3.90 (2.21–5.59)
Total (95% CI)			**593**			**2342**	**100**	**3.96 (2.57–5.35)**

SD, standard deviation; CI, confidence interval.
Heterogeneity: $Chi^2 = 30.67$; $df = 11$ ($P < 0.001$) $I^2 = 64\%$.
Test for overall effect: $Z = 5.59$ ($P < 0.001$)

(Fixed OR 1.89, 95% CI 1.28–2.81, $n = 832$, $P < 0.01$). (Fig. 2C)

A history of cerebrovascular accident (CVA) or transient ischemic attack (TIA) was assessed in 7 studies.[11,15,19,20,21,22,24] The incidence of POD was significantly higher in patients with a history of CVA/TIA; 22.4% vs. 14.3% (Fixed OR 2.20, 95% CI 1.68–2.88, $n = 2339$, $P < 0.001$). (Fig. 2D)

Renal failure was assessed in 8 studies[11,18,19,20,22–24,26] and poorly defined varying from an estimated GFR < 60 mL/min x 1.73m^2 to end stage renal failure with or without the need for renal replacement therapy. The incidence of POD was significantly higher in patients with compared to without renal failure: 24.6% vs. 15.9%, respectively (Fixed OR 1.61, 95% CI 1.19–2.17, $n = 2101$, $P = 0.002$). (Fig. 2E).

Psychosocial functioning

The relationship between cognitive impairment and depression and POD was studies in several studies. However, because of heterogeneity of assessment tools, no pooled analysis could be made.[11–15,18,19,24]

Laboratory abnormalities

Five studies analysed pre-operative haemoglobin (Hb),[12,18,19,23,26] as risk factor of which four could be pooled.[12,19,23,24] In meta-analysis a lower Hb level was considered a risk factor for POD with a mean of 11.9 g/dL vs. 12.6 g/dL in those without POD (fixed MD -0.76, 95% CI -1.04 to -0.47, $n = 1107$, $P < 0.001$). (Table IV)

Intra-Operative Risk Factors

Anesthesia

In 8 studies the association between type of anesthesia and POD was analysed.[11,15,16,18,19,20,23,26] In one study the effect of general, regional and local anesthesia was evaluated.[15] In three studies the effect of epidural analgesia and general anesthesia was evaluated,[11,20,23] while the remaining studies only distinguished between general anesthesia and any other combination.[16,18,19,26] Regional anesthesia (epidural/spinal) had a protective effect on the occurrence of POD as compared to other types of anesthesia (local/general) (Fixed OR 0.60; 95% 0.37–0.96, $P = 0.03$) (Fig. 3A)

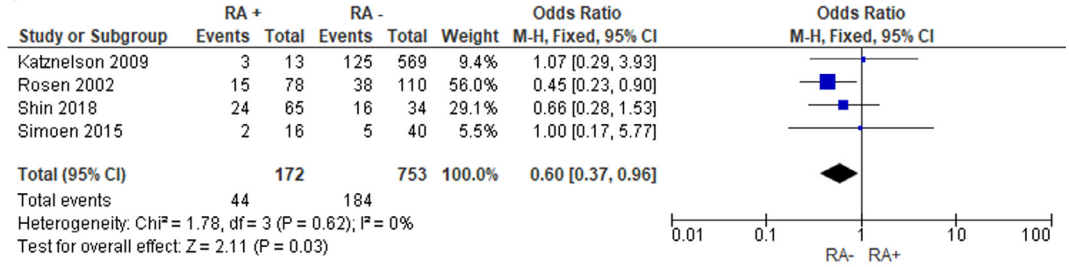
Duration and type of surgery

In 9 studies the association between the duration of surgery and the incidence of POD was studied, and duration of surgery was proven to be a risk factor for POD.[12,14,16,18,19,21–23,26] The mean duration of surgery was 251 min. in the POD group versus 201 min. in the non-POD group (Random MD 15.68; 95% CI 2.79–28.57, $n = 1887$, $P = 0.02$). (Table V)

In six studies on patients undergoing abdominal aortic aneurysm (AAA) repair the incidence of POD was significantly higher after open compared to endovascular surgery.[14–16,19,24] (Fixed OR 4.99, 95% CI 3.10–8.03, $n = 1032$, $P < 0.001$). (Fig. 3B)

When open AAA repair was performed, the aortic cross clamping time proved an additional risk factor

(a)



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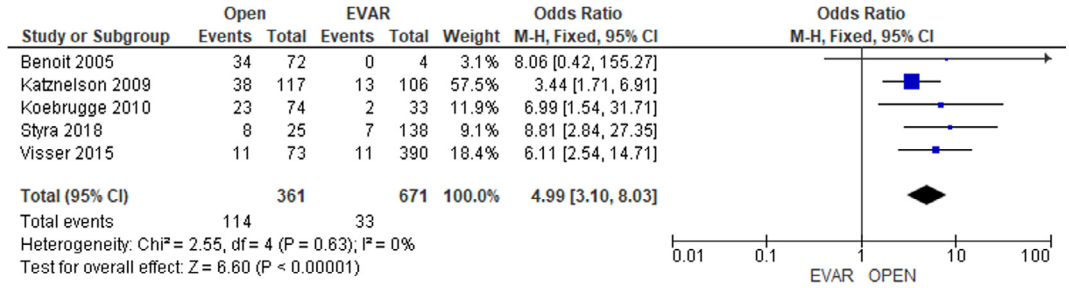

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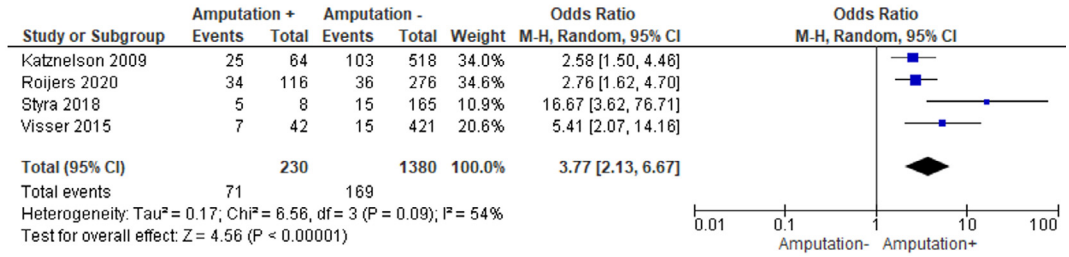

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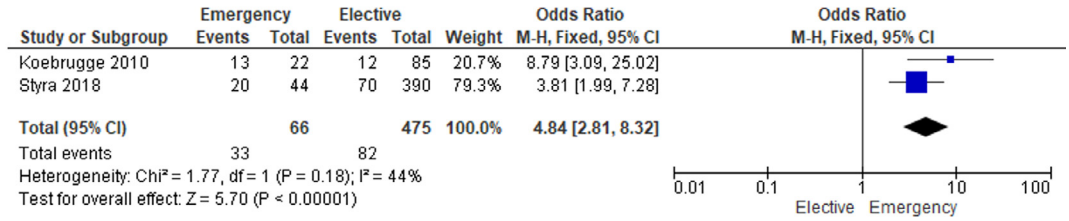

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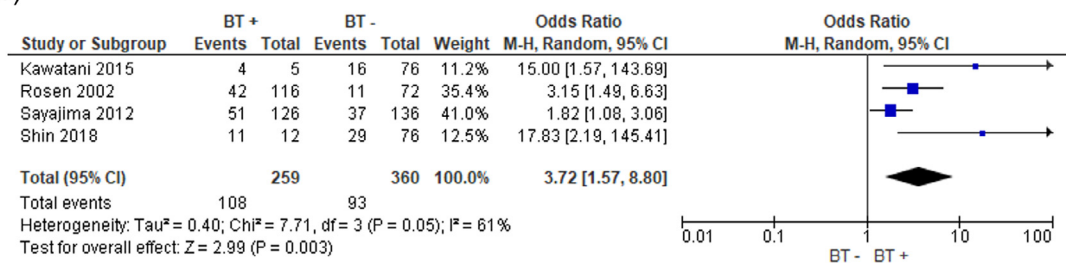

Fig. 3. (A) The association between regional anesthesia (RA) and delirium. (B) The association between open aorta surgery and delirium. (C) The association between amputation surgery and delirium. (D) The association between emergency surgery and delirium. (E) The association between need for blood transfusion (BT) and delirium.

Table IV. The association between pre-operative low Hb and delirium.

Study	Delirium present			Delirium absent			Weight (%)	Mean difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Böhner 2003	13.7	1.8	60	14.3	1.4	93	28.7	-0.60 (-1.14—0.06)
Visser 2015	12.7	2.8	22	13.5	4.2	441	5.4	-0.80 (-2.03–0.43)
Shin 2018	10.3	1.5	40	10.6	1.5	59	22.9	-0.30 (-0.90–0.30)
Roijers 2020	11	1.6	70	12.1	2.1	322	42.9	-1.10 (-1.54—0.66)
Total (95% CI)			**192**			**915**		**-0.76 (-1.04—0.47)**

SD, standard deviation; CI, confidence interval.
Heterogeneity: Chi² = 4.89; df = 3 (P = 0.18) I² = 39%.
Test for overall effect: Z = 5.15 (P < 0 .001)

Table V. The association between duration of surgery and delirium.

Study	Delirium present			Delirium absent			Weight (%)	Mean difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Rosen 2002	304.0	147.0	53	288.0	160.0	135	5.8	16.00 (-31.90–63.90)
Böhner 2003	178.0	118.0	60	148.0	63.0	93	10.1	30.00 (-2.49–62.49)
Benoit 2005	169.0	64.0	34	173.0	49.0	68	14.0	-4.00 (-28.46–20.46)
Koebrugge 2010	229.0	87.0	25	186.0	70.0	82	8.4	43.00 (5.68–80.32)
Sasajima 2012	390.0	205.0	88	343.0	195.0	211	5.3	47.00 (-3.27–97.27)
Visser 2015	242.8	131.3	22	209.3	109.2	441	4.5	33.50 (-22.30–89.30)
Sugimoto 2015	259.7	71.2	46	242.1	57.3	349	15.8	17.60 (-3.84–39.04)
Kawatani 2015	122	41.7	20	102	37.3	61	16.4	20.00 (-0.53–40.53
Shin 2018	110.4	34.3	40	117.5	46.6	59	19.7	-7.10 (-23.05–8.85)
Total (95% CI)			**388**			**1499**	**100**	**11.32 (2.54–10.10)**

SD, standard deviation; CI, confidence interval.
Heterogeneity: Chi² = 153.56; df = 14.26 (P = 0.08) I² = 44%.
Test for overall effect: Z = 2.38 (P = 0.02)

Table VI. The association between aortic cross clamp time and delirium.

Study	Delirium present			Delirium absent			Weight (%)	Mean difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Böhner 2003	41.6	21.4	60	33.1	16.9	93	71.7	8.50 (2.09–14.91)
Benoit 2005	70.5	24.6	34	63.8	25.1	68	28.3	6.70 (-3.50–16.90)
Total (95% CI)			**94**			**161**	**100**	**7.99 (2.56–13.42)**

SD, standard deviation; CI, confidence interval.
Heterogeneity: Chi² = 0.09; df=1 (*P* = 0.77) I² = 0%.
Test for overall effect: Z = 2.88 (*P* < 0.01)

in two studies[12,14] (fixed MD 7.99, 95% CI 2.56–13.42, *n* = 255, *P*< 0.01). (Table VI)

When all types of vascular surgery were included, amputation surgery was found to be the most important risk factor.[15,19,24,26] (random OR 3.77, 95% CI 2.13–6.67, *n* = 1610, *P*< 0.001). (Fig. 3C)

The association between emergency surgery and POD was assessed in two studies[16,24] and proved a risk factor for POD (Fixed OR 4.84, 95% CI 2.81–8.32, *n* = 541, *P*< 0.001). (Fig. 3D)

Blood loss and infusion

Blood loss was assessed in six studies.[11,12,16,18,21,23] Patients developing POD had more blood loss compared to the non-POD group (1633 ml vs. 1050 ml, random MD 496.5, 95% CI 84.51–908.44, *n* = 1405, *P*< 0.02). (Table VII). In line with this finding, the need for blood transfusion was also a risk factor for POD.[11,18,22,23] (Random OR 3.72, 95% CI 1.57–8.80, *n* = 619, *P*< 0.01). (Fig. 3E).

Table VII. The association between blood loss and delirium.

Study	Delirium present			Delirium absent			Weight (%)	Mean difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Rosen 2002	1723.0	1629.0	53	1610.0	1869.0	135	16.8	113.00 (-427.13–653.13)
Böhner 2003	2042.0	2707.0	60	1199.0	1386.0	93	13.4	843.00 (102.39–1583.61)
Koebrugge 2010	2630.0	1915.0	25	1283.0	1144.0	82	12.6	1347.00 (556.55–2137.45)
Visser 2015	1135.3	1769.0	22	425.6	886.2	441	13.3	809.70 (-34.12–1453.52
Sugimoto 2015	2080.0	1131.6	46	1565.0	896	349	20.3	515.00 (174.75–855.25)
Shin 2018	190.8	136.7	40	211.9	150.4	59	23.5	-21.10 (-78.26–36.06)
Total (95% CI)			**246**			**1159**	**100**	**496.47 (84.51–908.44)**

SD, standard deviation; CI, confidence interval.
Heterogeneity: Chi²=28.99; df=5 (P < 0.001) I²=83%.
Test for overall effect: Z=2.36 (P = 0.02)

Table VIII. The association between ICU stay and delirium.

Study	Delirium present			Delirium absent			Weight (%)	Mean difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Rosen 2002	8.9	9.0	53	3.9	2.0	135	10.1	5.00 (2.55–7.45)
Böhner 2003	2.9	2.2	60	2.7	2.3	93	20.0	0.20 (-0.53–0.93]
Benoit 2005	1.4	2.4	34	0.6	0.7	68	19.5	0.76 (-0.06–1.58)
Koebrugge 2010	6.5	6.7	25	1.5	3.4	82	9.0	5.00 (2.27–7.73)
Visser 2015	3.0	1.6	22	2.3	0.7	441	20.3	0.70 (0.03–1.37)
Kawatani 2015	3.3	2.4	20	2.5	0.82	61	18.0	0.80 (-0.27–1.87)
Shin 2018	17.2	15.6	40	7.8	12.1	59	2.9	9.40 (3.66–15.14)
Total (95% CI)			**254**			**939**	**100**	**1.71 (0.65–2.76)**

SD, standard deviation; CI, confidence interval.
Heterogeneity: Chi² = 31.77; df = 6 (P < 0.001) I² = 81%.
Test for overall effect: Z = 3.16 (P < 0.01)

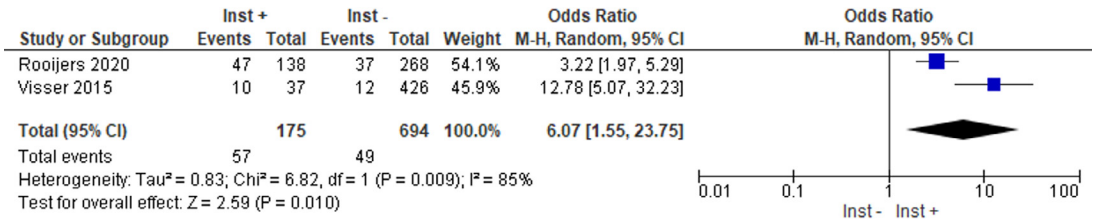

Fig. 4. The association between post discharge to a care facility (Inst) and delirium.

Postoperative Course

POD patients had a longer ICU stay: 6.2 days versus 3.1 days in non-POD patients.[11,12,14,16,19,22,23] (Random MD 1.71, 95% CI 0.65–2.76, 6 studies, $n=1193$, $P< 0.01$). Total hospital length of stay was 26.8 days in POD patients versus 21.3 days in non-POD patients. [11,12,14,16,19,22,23] (random MD 6.44, 95% CI 2.83–10.05, $n=1193$, $P< 0.001$). (Tables VIII and IX).

In two studies, the association between POD and discharge to a care facility was analysed and patients who had developed POD were more likely to be discharged to a care facility.[19,26] (Random MD 6.07; 95% CI 1.55–23.75, $n=869$, $P= 0.01$). (Fig. 4).

DISCUSSION

This study has identified several factors associated with the occurrence of POD. The incidence of POD in the included studies varied widely and ranged from 5% to 39%, depending on the type of surgery. These numbers correspond well with other types of surgery known for high incidences of POD. A systematic review including cardiac surgery patients in 2015 showed a range between 3% and 55%.[27] A recent study focusing primarily on elderly patients found an incidence of 21% in patients >65 years, and up to 33% in patients >80 years.[28] For patients undergoing gastrointestinal surgery (including cancer), POD is reported in 8.2–

Table IX. The association between total hospital length of stay and delirium.

Study	Delirium present			Delirium absent			Weight (%)	Mean difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Rosen 2002	14.8	11.0	53	9.2	5.0	135	20.2	5.60 (2.52–8.68)
Böhner 2003	10.9	6.0	60	9.3	8.4	93	21.6	1.60 (-0.68–3.88)
Benoit 2005	12.3	23.7	34	7.08	2.77	68	11.0	5.26 (-2.73–13.25)
Koebrugge 2010	26.3	17.1	25	9.4	7.4	82	12.7	16.90 (10.01–23.79)
Visser 2015	14.1	9.5	22	5.7	3.0	441	18.4	8.40 (4.42–12.38)
Kawatani 2015	14.5	11.9	20	9.9	5.3	61	15.5	4.60 (-0.78–9.98)
Shin 2018	94.8	132.1	40	98.4	87.1	59	0.6	-3.60 (-50.18–42.98)
Total (95% CI)			**254**			**939**	**100**	**6.44 (2.83–10.05)**

SD, standard deviation; CI, confidence interval.
Heterogeneity: $Chi^2 = 22.90$; $df = 6$ ($P < 0.001$) $I^2 = 74\%$.
Test for overall effect: $Z = 3.50$ ($P < 0.001$)

54.4%.[29] In orthopaedic surgery, the incidence of delirium after hip fracture repair in the elderly varies between 12% and 56%.[30] Remarkably, in all groups of patients the risk factors are common, with the most important risk factors being older age and multiple comorbidities. The increased incidence of POD after vascular surgery shows similarities with elderly patients, in which the incidence can be as high as 73%.[31–34] This shows that, independent of high age, vascular surgery patients should be considered as frail, and as a result have high risk for developing POD.[35–37] In addition to the growing awareness and pre-emptive care for these vulnerable patients, preventing POD is becoming an important part of hospital safety. As a result, a decreasing POD incidence is noticed across all disciplines over the last few years.[16,38,39]

In this meta-analysis, effect sizes were used to compare and systematically analyse different risk factors for POD after vascular surgery. After pooling individual risk factors, various preoperative risk factors were identified that is, age, hypertension, DM, hearing impairment, history of CVA/TIA, renal failure and Hb level. Intra-operative risk factors were duration of surgery, open AAA repair, aortic cross clamping time, amputation surgery, emergency surgery and blood loss and transfusion. Regional anesthesia had a protective effect on the occurrence of POD.

Our study was not the first systematic review and meta-analysis evaluating risk factors for POD after vascular surgery. Four similar reviews have been published in recent years.[40–43] However, those reviews were written in 2016 and 2017 and therefore became somewhat dated. Over the last years, there has been a lot of attention for POD in (vascular) surgery and therefore, studies succeed each other at a tremendous rate. As a result, in our review 4 of the 16 included studies were recently published, and could thus be added to our analysis. In addition, we also looked critically at potential data overlap due to duplicate publications and data sets, making the results more reliable and robust. Although we did include more studies, risk factors identified broadly correspond with the previous publications. The previous publications also found age to be an important risk factor and despite the fact that they all had a different way of measuring comorbidity (either as one entity or separately), they all found that patients suffering from multiple diseases had an increased risk of POD.

Age was considered a risk factor for POD in 8 of the 12 studies (67%). However, what was considered elderly or increased age was poorly defined and variable in these studies and a clear cut off point was lacking. Most studies had no restriction with regard to age, but the mean age was usually above 60 years. Although a uniform correlation between age and POD could not be determined, elderly patients tend to develop POD much more frequent. Homeostenosis, the phenomenon of reduction of homeostatic reserve which occurs with aging, may be an underlying cause. Accordingly, aging is associated with age-related cerebral changes in stress-regulating neurotransmitters, brain-blood flow decline, decreased vascular density and neuron loss.[44,45] This explains why the aging process itself is associated with some degree of cognitive decline and increased risk for POD in vascular surgery patients.

Hypertension, DM and history of CVA/TIA are common comorbidities, all of which lead or contribute to the onset of atherosclerosis, the common denominator of vascular surgery patients and in itself a risk factor for POD.[45] All those factors individually have proven to be a risk factor for POD, which is in line with the current literature.[45,46]

Although a lower Hb level proved a significant risk factor for developing POD, the small differences in actual Hb level will most likely have no effect on clinical practice. But these results do affirm that large amounts of blood loss or transfusion should be avoided in already frail vascular surgery patients.

Unfortunately, no studies evaluated the role of acetylcholinesterase inhibitors. Acetylcholinesterase inhibitors block the breakdown of acetylcholine, a neurotransmitter that has its influence on both the central and peripheral nervous system and is an important substrate for the modulation of cognition. It has been shown that acetylcholinesterase inhibitors are effective in patients with vascular dementia and Alzheimer's disease combined with cerebrovascular disease. Evidence suggests that in the brain of patients with delirium, the normal activity of the cholinergic system is also disrupted. Also, anticholinergics can precipitate delirium. This suggests that there might be a positive effect of acetylcholinesterase inhibitors on delirium.

In 2016, a review was performed including 7 RCT's that evaluated the use of acetylcholinesterase inhibitors in delirium in older (>60 years) patients. They concluded that there was no benefit for the use of acetylcholinesterase inhibitors in reducing delirium incidence.[47]

There is a huge variation in assessment tools and techniques for determining "cognitive impairment". The German research group of Böhner showed that low scores on the Folstein Mini-Mental State Examination (MMSE) confer a significant higher risk for POD. Minden et al. used telephone interviews for cognitive status, Visser et al. the Groningen Frailty Indicator, Sasajima et al. the Hasegawa's dementia scale and Styra et al the Montreal cognitive Assessment score. Furthermore, the Global Assessment Scale (GAS), the General Severity Score (ASGS), and the Brief Psychiatric Rating Scale (BPRS) were also used to evaluate psychosocial functioning and cognitive status.[12] Collectively, these studies show that cognitive impairment is a risk factor for POD and regardless of the tool, preoperative cognitive impairment should be considered an important risk factor for the development of POD.

Independently of the tool used, the goal is to pre-operatively identify the patients at highest risk for developing POD. For those patients, special programs to reduce the incidence and duration of POD can be initiated such as in-hospital geriatric medicine consultation, attention for active visual, hearing and cognitive impairment and prevent unnecessary immobility and maintaining a normal sleep/wake cycle.[48] Also, recent studies have shown that a prehabilitation program, including interventions to improve patients' physical and mental health pre-operatively, can decrease the incidence of POD who could benefit from special programs to reduce the incidence and duration of POD.[49]

A number of critical considerations pertaining our study can be made. A pooled analysis leads to some significant outcomes that are of little clinical relevance, for example the small differences in aortic cross clamping time, and caution is required when interpreting these findings. Tabulating results was challenging because of differences in the definitions, measurements and cut-off points of some risk factors. For example, there was no standardised definition of hypertension, depression, cognitive impairment and neurological disorders. Additionally, some missing data could enhance the risk of bias. Also worth noting is that a number of dominant research groups have published multiple articles on this topic. We chose to include only the study with the highest number of patients to obtain the highest statistical power and lower the risk of heterogeneity. However, by doing so the possibility exists that we have missed some patients and introduced a selection bias. This risk seems justified by us because otherwise duplicate patients would have been included in the pooled analysis which can result in an inappropriate weighting of the study results.[50] Although it is plausible that several risk factors interfere with each other, we could not adjust for these confounding variables. Nevertheless, we did identify several important risk factors all associated with delirium. A next step would be to study whether a combination of these risk factors is associated with POD, and can be used as a prediction tool. In order to do so a meta regression with mediation analysis is needed, but this is not the purpose of this study. However when a number of these risk factors are present or expected proactive geriatric consultation and multicomponent prevention and treatment strategies, such as the Hospital Elder Life Program program, should be started.[51] Also, over the recent years eHealth programs have been implemented. They have shown to improve clinical outcomes by educating patients preoperatively, and provide monitoring in the postoperative course.[52]

Medication use is a risk factor for POD which can both be a predisposing factor and an inducer. A recent review focusing on the influence of medication on POD found a significant association between beta-blocker use in vascular surgery.[53]

Also, the preoperative use of psychoactive medication was associatied with 7-fold higher risk of POD. Unfortunately, we could not include medicine use in the meta-analysis since only a few studies included it as a risk factor. Only one study included beta-blockers, and concluded it to be a contributing factor.[15] Regarding psychotropic drugs, different types were considered psychotropic (benzodiazepines, hypnotics, antidepressants and antipsychotics) and therefore no pooled analysis was possible.[11,14,24]

Although we know from the literature that both short- and long-term outcomes are worse in patients who develop POD, unfortunately most studies did not evaluate long- term outcome. Especially in this vulnerable group of patients, factors as type of care facility three or six months after surgery and cognitive status are of great importance for preservation of quality of life and self-image. These are items that should receive a lot more attention in the future, especially as this is often part of Patient Reported Outcome Measures and health related quality of life.[54]

In conclusion, POD after vascular surgery is a frequent complication and effect-size pooling supports the concept that POD is a complex heterogeneous disorder with multiple risk factors. Only a few studies have focused on POD in vascular surgery patients and this meta-analysis identified a wide range of risk factors, with varying clinical applicability. Based on our findings, a subgroup of high-risk patients who could benefit from preventive strategies can be identified.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.avsg.2021.03.034.

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