Impact of septic cerebral embolism on prognosis and therapeutic strategies of infective endocarditis: a retrospective study in a surgical centre

Valentina Scheggi1,5*, Silvia Menale2,5, Barbara Tonietti6, Costanza Bigiarini1,5, Jacopo Giovacchini2,5, Stefano Del Pace2,5, Nicola Zoppetti4, Bruno Alterini1,5, Pier Luigi Stefàno3,5 and Niccolò Marchionni2,5

Abstract

Background: Infective endocarditis still has high mortality and invalidating complications, such as cerebral embolism. The best strategies to prevent and manage neurologic complications remain uncertain. This study aimed to identify predictors of cerebral septic embolism and evaluate the role of surgery in these patients in a real-world surgical centre.

Methods: We retrospectively analyzed 551 consecutive patients admitted to our department with a definite diagnosis of non-device-related infective endocarditis; of these, 126 (23%) presented a neurologic complication.

Results: Cerebral embolism was significantly more frequent in patients with large vegetations ($p = 0.004$), mitral valve infection ($p = 0.001$), and Staphylococcus aureus infection ($p = 0.025$). At multivariable analysis, only vegetation length was an independent predictor of cerebral embolism (HR per unit 1.057, 95% CI 1.025–1.091, $p = 0.001$), with a best predictive threshold of 10 mm at ROC curve analysis (AUC 0.54, $p = 0.001$). Patients with neurologic complications were more often excluded from surgery despite an indication to it (16% vs 8%, $p = 0.001$). If eligible, they were treated within two weeks from diagnosis in similar proportions as patients without cerebral embolism with a similar survival rate. Predictors of mortality were hemorrhagic lesions ($p = 0.018$), a GCS < 14 ($p = 0.001$) or a severe degree of disability ($p = 0.001$) at presentation. The latter was the only independent predictor of mortality at multivariable analysis (HR 2.3, 95% CI 1.43–3.80, $p = 0.001$).

Conclusions: The present study highlights the prognostic value of functional presentation and the safety of cardiac surgery, when feasible, in patients with cerebral septic embolism.

Keywords: Endocarditis, Mortality, Prognosis, Infective endocarditis, Cerebral embolism, Outcome, Surgery

Background

Despite recent diagnostic and therapeutic advances, the mortality rate of infective endocarditis (IE) still exceeds 20% in-hospital [1] and 30% at 3 years [2]. Neurologic events complicate 10–40% of left-sided IE and include embolic cerebrovascular complications, intracranial haemorrhage, ruptured mycotic aneurysm, transient ischaemic attack, meningitis, encephalopathy and brain
surgery, medical therapy for the absence of surgical indi-
term mortality was adjusted for the treatment received:
Multivariable analysis of all-cause in-hospital and long-
GFR 45–59; Moderate GFR 30–44; Severe GFR 15–29).
valvular dysfunction, vegetation length, EUROSCORE
infection, the paravalvular extension of infection, severe
conditions. Age, gender, history of drug abuse, the micro-
cation or exclusion from surgery for prohibitive clinical
infection on cardiac devices other than valve prosthesis.
Data for analysis were retrieved from electronic hospita-
charts and were fully anonymized. The local Ethics Com-
Committee (Regional Ethics Committee of Tuscany for Ex-
Committee (Regional Ethics Committee of Tuscany for Ex-
Medicine, Section: AREA VASTA CEN-
clinics and were fully anonymized. The local Ethics
accordance with Italian laws for observational studies, granted
waiver of informed consent from study participants. We
followed the current international IE guidelines for diag-
work-up and treatment strategies and all methods
were performed in accordance with them [4]. Brain CT
or MR were performed in 352 (64%) patients, either for
neurologic symptoms (89) or for the screening of embo-
ism in asymptomatic patients (263). In patients with
cerebral embolism (126), we reported the site of embo-
the Glasgow Coma Scale (GCS) and the Barthel index [6]
Of 551 patients with IE in the registry, 126 (23%) had a
neurologic complication. The median follow-up was
Follow‑up
We calculated the follow-up duration from the time of
IE diagnosis. A structured phone interview updated the
follow-up of all patients to March 2022.
Study endpoints
Identification of predictors of cerebral embolism and
mortality in patients with neurologic complications of IE
were the primary study endpoints.
Statistical analysis
We used the chi-square and the Mann–Whitney or
Kruskal–Wallis tests to compare respectively proportions
and continuous variables with normal or non-normal
distribution. We performed univariable and multivari-
able analyses using logistic regression and general linear
models. We used the Kaplan–Meier method to estimate
the univariate survival analysis and the Cox regression to
identify the multivariable associations with mortality and
estimate their hazard ratio with 95% confidence interval.
All tests were 2-sided, and statistical significance was
defined as a p-value < 0.05. We performed the analyses
with SPSS 23.0 and R 3.6.3.
Results
Patient characteristics
Of 551 patients with IE in the registry, 126 (23%) had a
neurologic complication. The median follow-up was
3.4 years (95% CI 3.2–3.6). The main demographic, cli-
cal, echocardiographic and microbiologic characteris-
tics of the cohort by the presence or absence of cerebral
embolism are reported in Table 1.
Cerebral embolism was significantly more frequent in
patients with large vegetations (p = 0.004), mitral valve
infection (p = 0.001), and Staphylococcus aureus infec-
tion (p = 0.025). Patients with neurologic complications
also had a significantly higher left ventricular ejection
fraction and a lower proportion of severe valvular dys-
function. Such a difference is the probable consequence
of a referral to a surgical centre since, beyond embolic
complications, surgery for IE is indicated by heart failure
or severe valvular dysfunction [4]. At multivariable anal-
ysis, only vegetation length was an independent predictor
of cerebral embolism (HR 1.057, 95% CI 1.025–1.091,
p = 0.001), with a best predictive threshold of 10 mm
length at ROC analysis (AUC 0.54, p = 0.001).
Table 1: Demographic, clinical, echocardiographic and microbiologic characteristics of the study population, by presence of cerebral embolism

| Cerebral embolism | p value |
|--------------------|---------|
| No (N = 425)       | Yes (N = 126) |

Age (years, median ± IQR) 69 ± 22 69 ± 19  NS
Female gender (N, %) 140 (33.8%) 45 (36.9%)  NS
BMI (median ± IQR) 24.2 ± 5.2 24.0 ± 4.5  NS
Diabetes (N, %) 81 (19.1%) 23 (18.3%)  NS
Dyslipidemia (N, %) 116 (29.3%) 37 (31.6%)  NS
Hypertension (N, %) 250 (59.1%) 73 (57.9%)  NS
Renal failure (N, %) 101 (23.8%) 31 (24.6%)  NS
Male gender (N, %) 235 (55.3%) 60 (47.6%)  NS
Severe (N, %) 13 (3.1%) 5 (4.0%)  NS
Dialysis (N, %) 15 (3.5%) 2 (1.6%)  NS
Cancer (N, %) 95 (22.4%) 22 (17.5%)  NS
PM (N, %) 56 (13.2%) 11 (8.7%)  NS
Oral anticoagulant therapy (N, %) 120 (28%) 40 (32%)  NS
Drug abuse (N, %) 47 (11.1%) 13 (10.3%)  NS
Vegetation length (mm, median ± IQR) 10 ± 11 11 ± 10 0.004
Site of infection
Aortic valve (N, %) 235 (55.3%) 60 (47.6%) 0.001
Mitral valve (N, %) 149 (35.1%) 64 (50.8%)  NS
Tricuspid valve (N, %) 41 (9.6%) 2 (1.6%)  NS
Prosthetic valve (N, %) 172 (40.6%) 50 (39.7%)  NS
Double valve infection (N, %) 69 (16.2%) 23 (18.3%)  NS
Severe valvular dysfunction (N, %) 213 (50.1%) 47 (37.3%) 0.015
Paravalvular extension (N, %) 90 (21.2%) 26 (20.6%)  NS
EF (%median ± IQR) 58 ± 11 60 ± 10 0.008
TAPSE (mm, median ± IQR) 21 ± 6 19 ± 7  NS
EuroSCORE II (median ± IQR) 7 ± 12 8 ± 20  NS
Germ (N, %)
Streptococci 69 (16.2%) 20 (15.9%) 0.025
S. bovis 37 (8.7%) 4 (3.2%)
Staphylococcus aureus 69 (16.2%) 34 (27.0%)
Coagulase negative staphylococci 56 (13.2%) 12 (9.5%)
Enterococci 88 (20.7%) 18 (14.3%)
Negative cultures 77 (18.1%) 26 (20.6%)
Other 29 (6.8%) 12 (9.5%)

BMI: body mass index, PM: pacemaker, EF: ejection fraction, TAPSE: tricuspid annular plane systolic excursion.

Surgical treatment and mortality

Of 551 patients with IE, 431 (78%) underwent surgery, 60 (11%) received only medical therapy because of the absence of surgical indication, and 60 (11%) were excluded from surgery, despite surgical indication, because of prohibitive general conditions.

Table 2: Therapeutic strategies and mortality of patients with infective endocarditis, by presence of cerebral embolism

| Cerebral embolism | p value |
|--------------------|---------|
| No (N = 425)       | Yes (N = 126) |

Treatment (N, %)
Excluded from surgery despite indication 40 (9.5%) 20 (15.8%) 0.002
Surgery 329 (77.4%) 102 (81.0%)
No indication for surgery 56 (13.1%) 4 (3.2%)
Thirty-day mortality (N, %) 36 (8.5%) 13 (10.3%) NS
Three-year mortality (N, %) 135 (31.8%) 48 (38.1%) NS

Three-year mortality was not significantly different between the two groups (p = 0.009). Compared to those without, patients with neurologic complications were more often excluded from surgery despite an indication for it (Table 2). As shown in Table 3, severe disability (i.e. Barthel index score class 3) was the main reason for denying surgery. When eligible, patients with or without neurologic complications were operated upon within two weeks of IE diagnosis in similar proportions (70% vs 72%) and with similar survival rates for each treatment group (i.e. surgery; medical therapy for the absence of surgical indication; excluded from surgery because of prohibitive general conditions; Fig. 1) and for patients undergoing early surgery (Fig. 2).

Hemorrhagic transformation (p = 0.018), GCS ≤ 14 (p = 0.001) or Barthel index score < 40 (i.e. severe disability; p = 0.001) at presentation were univariate predictors of mortality in IE patients with cerebral embolism. Of these, only the Barthel index latter was kept in the final multivariable model (HR 2.4, 95% CI 1.47–3.95, p = 0.001), together with known adverse prognostic factors of infective endocarditis such as age (HR 1.036 for each increasing year, 95% CI 1.024–1.050), double valve infection (HR 2.27, 95% CI 1.59–3.23), EUROSCORE II (HR 1.015 per unitary increase, 95% CI 1.009–1.021), and exclusion from surgery (HR 4.82, 95% CI 2.42–9.58) [7].

Figure 3 shows the survival curves of patients with cerebral embolism stratified by levels of disability, and Fig. 4 shows the same curves by levels of disability and treatment, highlighting the independent prognostic impact of disability itself.

Discussion

Our data failed to confirm the independent, negative prognostic impact demonstrated in other clinical series of cerebral embolisms complicating IE [8]. This probably depends on different inclusion criteria since we also enrolled asymptomatic or mildly symptomatic events. Instead, we found that the onset and the severity of functional disability is independently associated with the risk...
of all-cause death, even after adjusting for a series of instrumental and demographic variables. The value of Barthel index in patients with ischemic stroke has been largely demonstrated [9], while only two studies [5, 10] included it to evaluate patients with neurologic complications of IE. Neither of them, however, used the Barthel index to explore the association of disability with mortality. Besides the anatomical characterization of a cerebral event, the functional status is a major determinant of prognosis and should guide therapeutic strategies. The same neurologic event may hesitate to different levels of disability that, at least in large part, depend on the functional status before the acute event. The Barthel index gives a comprehensive measure of the residual autonomy, which should be considered to avoid futility in terms not only of the quality of life but of survival rate. Conversely, patients with preserved functional status should receive prompt cardiac surgery as indicated.

Table 3  Clinical and anatomical characteristics of patients with cerebral embolism, by therapeutic strategy

| Treatment | Excluded from surgery (N = 20) | Surgery (N = 102) | No indication for surgery (N = 4) |
|-----------|---------------------------------|-------------------|---------------------------------|
| Age (years, median ± IQR) | 73 (66–79) | 66 (62–72) | 67 (36–78) |
| Dysambility at admission (N, %) | | | |
| Mild | 4 (21,1%) | 56 (62,9%) | 3 (75%) |
| Moderate | 1 (5,3%) | 16 (18,0%) | 0 (0%) |
| Severe | 14 (73,7%) | 17 (19,1%) | 1 (25%) |
| Neurologic symptoms (N, %) | | | |
| Mild | 18 (90,0%) | 69 (75,0%) | 2 (50%) |
| Moderate | 9 (45,0%) | 25 (24,5%) | 0 (0%) |
| Site of cerebral lesion (N, %) | | | |
| Basal nuclei | 1 (5,3%) | 4 (4,3%) | 1 (25%) |
| Cerebral lobes | 12 (63,2%) | 61 (65,6%) | 2 (50%) |
| Cerebellum | 0 (0,0%) | 3 (3,2%) | 0 (0%) |
| Multiple sites | 6 (31,6%) | 25 (26,9%) | 1 (25%) |

Fig. 1  Kaplan–Meier analysis of survival probability of 551 patients with infective endocarditis with (Y) or without (N) cerebral septic embolism, divided for therapeutic strategy: excluded from surgery (E), surgery (S), medical therapy (M)
In accordance with previous studies [3, 5, 10], our data demonstrated the safety of early surgery since patients operated on within two weeks of IE diagnosis had similar survival in the presence or absence of neurologic complications. Interestingly, patients with neurologic complications treated after two weeks had a survival curve similar
to that of earlier surgery. This suggests that an individually tailored timing of surgery is the optimal strategy.

Finally, the prevention of embolism has probably the greatest impact on prognosis. We found that a vegetation length greater than 10 mm is an independent predictor of embolism. Guidelines [4] recommend (IIB, level of evidence C) surgery for the primary prevention of embolism, as the sole indication, for vegetations > 15 mm. Considering the potentially devastating consequences of even a single embolic cerebral event and the good results of surgery, we believe that the threshold to indicate surgery should be lowered, especially in patients with a low operative risk and a preserved functional profile as assessed by the Barthel index. Further studies on this issue are necessary.

Our study has some limitations: first, its retrospective nature; second, changes in the clinical management of IE may have occurred during the long study period. Third, it is a real-world single-centre experience. Finally, our study has a potential referral bias since we have conducted it in a high-volume surgical centre; therefore, the percentage of patients with a surgical indication may be regarded as disproportionately high.

Conclusions
In patients with neurologic complications of IE, the primary determinant of prognosis is the functional status after the event. Early surgery is safe for most patients, but an individually tailored program guarantees a similar prognosis for patients who need delayed surgery.

Acknowledgements
Authors are grateful to Fondazione A.R.Card Onlus for its unconditional support.

Author contributions
VS projected the study, analyzed and interpreted the data and wrote the manuscript. SM, JG, BT and CB collected the data for analysis and contributed writing the manuscript. NM revised the manuscript. NZ carried out the statistical analysis. PLS performed the surgical interventions. NM revised the final version of the manuscript. SDP and BA performed clinical follow-up and contributed for the clinical management of patients. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. All authors read and approved the final manuscript.

Funding
None to declare.

Availability of data and materials
The dataset used and analyzed during the current study is available from the corresponding author on reasonable request sharing the SPSS dataset.

Declarations
Ethics approval and consent to participate
The study was approved by the local ethics Committee (Regional Ethics Committee of Tuscany for Experimental Medicine, Section: AREA VASTA CENTRO, n. 12113, oss), that, in keeping with statements by the Italian Regulatory Authorities for retrospective, observational studies (https://www.garantepri vacy.it/ web/guest/home/docweb/-/docweb-display/docweb/5805552), granted a waiver of informed consent from study participants.
Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1 Division of Cardiovascular and Perioperative Medicine, Florence, Italy.  
2 Division of General Cardiology, Florence, Italy.  
3 Division of Cardiac Surgery, Florence, Italy.  
4 Institute of Applied Physics “Nello Carrara” (IFAC), National Research Council, Florence, Italy.  
5 Cardiothoracicvascular Department, Azienda Ospedaliero-Universitaria Careggi and University of Florence, Florence, Italy.  
6 Health Management Direction, Azienda Ospedaliero-Universitaria Careggi and University of Florence, Florence, Italy.

Received: 31 March 2022  Accepted: 10 June 2022  
Published online: 17 June 2022

References
1. Gabbieri D, Dohmen PM, Linneweber J, Grubitzsch H, von Heymann C, Neumann K, et al. Early outcome after surgery for active native and prosthetic aortic valve endocarditis. J Heart Valve Dis. 2008;17(5):508.
2. Dohmen PM, Binner C, Mende M, Daviewala P, Etz CD, Borger MA, et al. Gender-based long-term surgical outcome in patients with active infective aortic valve endocarditis. Med Sci Monit. 2016;18:22.
3. Rossi M, Gallo A, De Silva RJ, Sayeed R. What is the optimal timing for surgery in infective endocarditis with cerebrovascular complications? Interact Cardiovasc Thorac Surg. 2012;14(1):72–80.
4. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta J-P, Del Zotti F, et al. ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC) En-dorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015;36:36.
5. Ruttmann E, Abfalterer H, Wagner J, Grimm M, Muller L, Bates K, Ulmer H, Bonaros N. Endocarditis-related stroke is not a contraindication for early cardiac surgery: an investigation among 440 patients with left-sided endocarditis. Eur J Cardiothorac Surg. 2020;58(6):1161–7.
6. Dewing J. A critique of the Barthel Index. Br J Nurs. 1992;1(7):325–9.
7. Scheggi V, Merilli I, Marcucci R, Del Pace S, Olivotto I, Zoppetti N, Ceschia N, Andrei V, Alterini B, Stefano PI, Marchioni N. Predictors of mortality and adverse events in patients with infective endocarditis: a retrospective real world study in a surgical centre. BMC Cardiovasc Disord. 2021;21(1):28.
8. Chu VH, Cabell CH, Benjamin DK Jr, Kuniholm EF, Fowler VG Jr, Engemann J, Sexton DJ, Corey GR, Wang A. Early predictors of in-hospital death in infective endocarditis. Circulation. 2004;109(14):1745–9.
9. Liu F, Tsang RC, Zhou J, Zhou M, Zha F, Long J, Wang Y. Relationship of Barthel Index and its Short Form with the Modified Rankin Scale in acute stroke patients. J Stroke Cerebrovasc Dis. 2020;29(9):105033.
10. Ruttmann E, Willet J, Ulmer H, Chevtschik O, Hofer D, Poewe W, Laufer G, Muller LC. Neurological outcome of septic cardioembolic stroke after infective endocarditis. Stroke. 2006;37(8):2094–9.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.