Acute heart failure after non-cardiac surgery: incidence, phenotypes, determinants and outcomes

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Aims

Primary acute heart failure (AHF) is a common cause of hospitalization. AHF may also develop postoperatively (pAHF). The aim of this study was to assess the incidence, phenotypes, determinants and outcomes of pAHF following non-cardiac surgery.

Methods and results

A total of 9,164 consecutive high-risk patients undergoing 11,262 non-cardiac inpatient surgeries were prospectively included. The incidence, phenotypes, determinants and outcome of pAHF, centrally adjudicated by independent cardiologists, were determined. The incidence of pAHF was 2.5% (95% confidence interval [CI] 2.2–2.8%); 51% of pAHF occurred in patients without known heart failure (de novo pAHF), and 49% in patients with chronic heart failure. Among patients with chronic heart failure, 10% developed pAHF, and among patients without a history of heart failure, 1.5% developed pAHF. Chronic heart failure, diabetes, urgent/emergent surgery, atrial fibrillation, cardiac troponin elevations above the 99th percentile, chronic obstructive pulmonary disease, anaemia, peripheral artery disease, coronary artery disease, and age, were independent predictors of pAHF in the logistic regression model.
Patients with pAHF had significantly higher all-cause mortality (44% vs. 11%, \(p<0.001\)) and AHF readmission (15% vs. 2%, \(p<0.001\)) within 1 year than patients without pAHF. After Cox regression analysis, pAHF was an independent predictor of all-cause mortality (adjusted hazard ratio [aHR] 1.7 [95% CI 1.3–2.2]; \(p<0.001\)) and AHF readmission (aHR 2.3 [95% CI 1.5–3.7]; \(p<0.001\)). Findings were confirmed in an external validation cohort using a prospective multicentre cohort of 1250 patients (incidence of pAHF 2.4% [95% CI 1.6–3.3%]).

Conclusions
Postoperative AHF frequently developed following non-cardiac surgery, being de novo in half of cases, and associated with a very high mortality.

**Graphical Abstract**

Incidence, phenotypes, determinants and outcomes of acute heart failure after non-cardiac surgery (pAHF)

- **Incidence:** 9164 patients, 11262 surgeries
- **Independent predictors of pAHF:**
  - Chronic HF
  - COPD
  - Diabetes
  - Anemia
  - Urgent/emergent surgery
  - PAD
  - Age
  - Atrial fibrillation
  - CAD
  - Cardiac troponin elevation
- **Mortality:**
  - 238 cases of pAHF (incidence 2.5%)
  - 139 pAHF in chronic HF (49%)
  - 144 de novo pAHF (51%)
  - aHR 1.7 [95% CI 1.3–2.2]
- **Readmission for AHF:**
  - 23 cases of pAHF (incidence 0.2%)
  - 22 pAHF in chronic HF (95%)
  - 1 pAHF de novo pAHF (5%)
  - aHR 2.3 [95% CI 1.5–3.7]

Incidence, phenotypes, determinants and outcomes of acute heart failure after non-cardiac surgery. aHR, adjusted hazard ratio; CAD, coronary artery disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; HF, heart failure; HFrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; PAD, peripheral artery disease; pAHF, postoperative acute heart failure; y, years.

**Keywords**
- Acute heart failure
- Heart failure
- Non-cardiac surgery
- Postoperative

**Introduction**

Acute heart failure (AHF) is the most common cause of urgent hospitalization, and is associated with high mortality and morbidity.\(^1\)–\(^7\)

Over the last decades, major efforts by interdisciplinary academic consortia, professional societies, and the pharmaceutical industry have provided important evidence regarding this complex heterogeneous syndrome.\(^1\)–\(^15\)

Recently, it has become apparent that AHF may not only be a major health burden as the primary diagnosis leading to hospitalization, but also if developing as a complication in patients hospitalized for other medical or surgical causes.\(^16\),\(^17\) It has been recently shown that, among patients admitted to the emergency department and hospitalized with AHF, 55% had AHF as a secondary diagnosis.\(^18\) AHF developing postoperatively (pAHF) in patients undergoing non-cardiac surgery is of particular concern, as cardiologists/internists are often not involved in patient care in this setting, which may lead to underdiagnosis and undertreatment. The high number of patients at high cardiovascular risk undergoing non-cardiac surgery each year, and the unexpectedly high 30-day mortality (reaching 21.5%) reported following non-cardiac surgery, further increase the clinical relevance of pAHF.\(^19\)–\(^24\) Unfortunately, little is known regarding the incidence, phenotypes, determinants and outcomes of pAHF. The incidence of pAHF has been estimated...
to range between 1% and 3.8% in retrospective studies or studies that evaluated pAHF as a part of a composite endpoint of major adverse cardiac events.\(^{17-20}\) Prospective studies specifically focusing on pAHF are needed.

The aim of this study was to assess the incidence, phenotypes, determinants, and outcomes of patients with adjudicated pAHF following non-cardiac surgery.

**Methods**

**Patients**

This is a secondary analysis within the BASEL-PMI study (NCT025 73532), an ongoing prospective study aiming at the detection and adjudication of cardiac complications following non-cardiac surgery using a perioperative myocardial infarction/injury (PMI) active surveillance and response programme in high-risk patients with routine measurements of pre- and postoperative cardiac troponin concentrations (online supplementary methods).\(^{22,23,3}\) In brief, consecutive patients aged ≥65 years OR ≥45 years with history of coronary artery disease (CAD), peripheral artery disease (PAD) or stroke undergoing major non-cardiac surgery at the University Hospital Basel or the Kantonsspital Aarau, both in Switzerland, as well as consecutive patients scheduled for arterial vascular surgery at the Heart Institute, University of Sao Paulo Medical School, Brazil, were prospectively enrolled before surgery. Patients were included if they had a planned hospital stay exceeding 24 h after a non-cardiac surgery (elective, emergency, or urgent). Patients with PMI received a cardiac evaluation including history, physical examination, 12-lead electrocardiogram, and possibly cardiac imaging to identify the PMI aetiology.\(^{22,23,3}\) Patients whose surgery had been cancelled and those who had undergone cardiac surgery in the 2 weeks preceding the operation were excluded. For this analysis, we excluded patients for whom adjudication of pAHF was not possible due to insufficient clinical data. Patients could be included in the study more than once, as long as the interval between the two operations was longer than 4 days. Repeated surgery was considered any surgery (elective or urgent) within 1 year of the first operation. For the 1-year follow-up analysis, patients were included only once, at the first enrolment. The investigation conforms with the principles outlined in the Declaration of Helsinki, the local ethics committees approved the protocol, patients provided written general consent to registration in a dedicated prospective database, and the study was performed in adherence to the STROBE guidelines for observational studies (online supplementary Table S1). Before surgery, cardiac risk was classified based on the Revised Cardiac Risk Index (RCRI), and surgical risk was classified as proposed by the European Society of Cardiology and the European Society of Anaesthesiology (ESC/ESA).\(^{2,3}\) The clinical management of patients was at discretion of the treating physicians (online supplementary methods). External validation was performed in an independent prospective, multicentre observational, cohort study in patients >50 years of age undergoing elective major non-cardiac surgery at seven hospitals in Sweden.\(^{24}\) No additional clinical criteria were needed for inclusion. Additional information about the validation cohort is shown in online supplementary methods.

**Central adjudication and diagnosis of postoperative acute heart failure**

The presence and phenotype of pAHF was centrally adjudicated by independent cardiologists according to current guidelines as an episode of AHF within 1 month after surgery (regardless if the patient was still in-hospital) based on symptoms and signs of AHF, chest X-ray, B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) plasma concentrations, and cardiac imaging including echocardiography.\(^{1,3}\) Additionally, the episodes of pAHF were classified according to the four phenotypes (acute decompensated heart failure [HF], acute pulmonary oedema, isolated right ventricular failure and cardiogenic shock), defined in the 2021 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic HF.\(^{1}\) Additional information about the diagnosis of pAHF in clinical routine is shown in online supplementary methods.\(^{1,3}\)

**Follow-up and outcomes**

Patients were followed by outpatient clinic consultations, phone, and/or contacting their primary care physician. Additionally, the study investigators requested reports from the general practitioners, treating facilities or death registries. Patients lost to follow-up were censored at last contact. Outcomes were centrally adjudicated by an independent physician. All-cause mortality within 1 year was the primary prognostic endpoint, and hospital readmissions due to AHF within 1 year was the secondary prognostic endpoint.

**Statistical analysis**

The incidence of pAHF was calculated with 95% confidence intervals (CI) overall and stratified by type of surgery. Comparisons between the baseline characteristics of patients with and without pAHF were performed using the chi-square test for categorical variables, which are shown as numbers and percentages, and the Mann–Whitney test for continuous variables, which are presented as medians and interquartile range (IQR).

**Risk factors for postoperative acute heart failure**

To determine the preoperative variables independently related to the occurrence of pAHF, a multivariable logistic regression model was constructed with pAHF within 1 month as the dependent variable. In the absence of established risk factors in this specific context of pAHF after non-cardiac surgery, variables with a p-value <0.1 in the univariable analysis were included in the model. Based on the number of events and the consensus requiring 10 events for independent variable compared in regression models, we could address all variables. The area under the receiver-operating characteristics curve (AUC) was used to quantify the accuracy of the RCRI, which was developed to estimate the risk of myocardial infarction, pulmonary oedema, cardiac arrest, and complete heart block, for predicting pAHF.\(^{2}\)

**Prognostic analysis**

We performed two multivariable Cox proportional hazards analyses with death and readmission due to AHF within 1 year as dependent variables, to determine adjusted hazard ratios (HR) for pAHF. Based on prior work and clinical relevance, the following covariates were included in the model for mortality: age, RCRI, urgency/emergency surgery, presence of PAD, atrial fibrillation, chronic obstructive pulmonary disease (COPD) and postoperative sepsis, pneumonia and stroke.\(^{2}\) In addition, as our analysis intended to quantify the association of pAHF with outcome, we further adjusted on chronic HF. For readmission due to AHF, we included in the multivariable model...
all clinically relevant variables by forced entry, including chronic HF. We stratified patients according to pAHF status and constructed Kaplan–Meier plots for 1-year mortality and readmission due to AHF. Curves were compared by the log-rank test. Additionally, in order to determine if there was an interaction with time to death, we constructed separate Kaplan–Meier plots for determining the mortality in the first month after pAHF, as well as for the period between 31 and 120 days.

Sensitivity analysis
We repeated the analysis for the incidence of pAHF, excluding the multiple inclusion cases (per patient analysis). Regarding the risk factors for pAHF, we performed sensitivity analysis to determine risk factors for de novo pAHF (by excluding patients with pAHF in CHF) and for pAHF in CHF (by excluding patients with de novo pAHF). In these regression models, the variable chronic HF was excluded. Additionally, we performed a post-hoc sensitivity analysis for the incidence and mortality of pAHF in patients undergoing elective and urgent (operation within 7 days) or emergency surgery (operation within 24 h).

Subgroup analysis
To evaluate the prognosis of patients with de novo pAHF versus patients with known chronic HF, patients were stratified into four groups (no HF, CHF without pAHF, CHF with pAHF, and de novo pAHF) and Kaplan–Meier plots for 1-year mortality and readmission due to AHF were constructed. Additionally, we post-hoc compared the prognosis of patients with de novo AHF and all patients with CHF (independent of the pAHF status). We also performed subgroup analysis in patients with or without postoperative clinically relevant arrhythmias, defined as any arrhythmia (including atrial fibrillation/flutter) that needed an intervention (medicaments or cardioversion).

Missing data are indicated in or below the respective tables and figures. No imputation was performed for missing values. A p-value of <0.05 was considered to indicate statistical significance. The statistical analyses were performed using SPSS v. 24 and R 3.6.x.

Results
Overall, 9164 patients undergoing 11 262 surgeries were included (online supplementary Figure S1), of which 9555 (84.8%) were older than 65 years. A total of 26 cases (0.2%) were excluded due to lack of data for pAHF adjudication. Postoperative AHF was adjudicated in 283 cases, resulting in an incidence of 2.5% (95% CI 2.2–2.8). Patients developing pAHF were older, more often had known cardiovascular disorders as well as non-cardiovascular comorbidities versus patients not developing pAHF (Table 1). Among patients with CHF, 10% developed pAHF, and among patients without a history of HF, 1.5% developed pAHF. Surgical urgency, surgical specialty and ESC/ESA surgical risk classification were associated with the incidence of pAHF, while the type of anaesthesia was not (online supplementary Table S2A). The incidence of pAHF was highest in patients undergoing vascular, thoracic, and orthopaedic surgeries (3.5%, 3.5%, and 3.4%, respectively), and in patients undergoing high-risk surgeries according to the ESC/ESA classification (4.5%). These findings were confirmed in the sensitivity analysis per patient (online supplementary Table S2B). Among the 8154 elective surgeries, the incidence of pAHF was 1.8% (95% CI 0.9–2.7) and among the 3108 urgent/emergency surgeries, the incidence of pAHF was 4.5% (95% CI 2.1–6.8).

Phenotypes of postoperative acute heart failure
Postoperative AHF most often occurred on postoperative day 2 (median day 4, IQR 1–11; online supplementary Figure S2). About half of pAHF cases (51%) occurred in patients without known HF (de novo pAHF), and 49% in patients with CHF. Preserved left ventricular ejection fraction (LVEF) was the dominant phenotype among de novo pAHF (72%), while a reduced LVEF was dominant among pAHF in chronic HF (43%) (Figure 1). Regarding the clinical presentation of pAHF, 220 cases (77.7%) were classified as ‘acute decompensated HF’, 23 (8.1%) as ‘acute pulmonary oedema’, 17 (6%) as ‘isolated right ventricular failure’, and 23 (8.1%) as ‘cardiogenic shock’. The length of stay was significantly longer in patients with pAHF than in patients without pAHF (median 14 days [IQR 8–26 days] vs. 7 days [IQR 4–11 days], p < 0.001).

Regarding the occurrence of atrial fibrillation as a possible precipitant factor for pAHF, 29 cases of pAHF (10%) had also high-rate atrial fibrillation needing intervention. In seven cases (24%), atrial fibrillation occurred the same day as the pAHF, in 2 (7%) within 72 h before the pAHF episode, and in 4 (14%) within 72 h after the pAHF episode.

The median NT-proBNP concentration (available in 24% of patients) was 7052 ng/L (IQR 3233–14 679 ng/L). A comparison between clinical characteristics of patients with and without NT-proBNP is shown in online supplementary Table S3.

Regarding high-sensitivity cardiac troponin T (hs-cTnT), 95% of patients with pAHF had hs-cTnT concentrations above the 99th percentile (14 ng/L) and 49% fulfilled the criteria for a PMI (additional information in online supplementary results).36
The use of HF medication is shown in online supplementary results.

Preoperative determinants of postoperative acute heart failure
Age, CHF, CAD, atrial fibrillation, PAD, diabetes mellitus, chronic myocardial injury, anaemia, COPD, and urgent or emergency surgery were independent preoperative determinants for the development of pAHF (Table 2). The type of anaesthesia was not a determinant of pAHF (p = 0.773). The independent predictors for de novo pAHF and pAHF in CHF are shown in online supplementary Table S4. The AUC of the RCRI for predicting pAHF was 0.73 (95% CI 0.70–0.76) and the AUC for predicting cardiac complications was 0.69 (95% CI 0.67–0.71; online supplementary Table S5).

Prognosis of postoperative acute heart failure
Among the 9164 patients included in this analysis, the 1-year follow-up was complete in 9114 patients (99.5%). A total of 1045

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Table 1 Baseline characteristics of patients with and without postoperative acute heart failure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All surgeries (n = 11262)</th>
<th>pAHF (n = 283)</th>
<th>No pAHF (n = 10979)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>6522 (58)</td>
<td>165 (58)</td>
<td>6357 (58)</td>
<td>0.903</td>
</tr>
<tr>
<td>Age (years), median (IQR)</td>
<td>73 (68–79)</td>
<td>79 (72–83)</td>
<td>73 (68–79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>2872 (26)</td>
<td>138 (49)</td>
<td>2734 (25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No insulin, n (%)</td>
<td>1781 (16)</td>
<td>74 (26)</td>
<td>1707 (16)</td>
<td></td>
</tr>
<tr>
<td>Insulin, n (%)</td>
<td>1091 (10)</td>
<td>64 (23)</td>
<td>1027 (9)</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>7641 (68)</td>
<td>221 (78)</td>
<td>7420 (68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>3430 (31)</td>
<td>167 (59)</td>
<td>3263 (30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral artery disease, n (%)</td>
<td>3187 (28)</td>
<td>129 (46)</td>
<td>3058 (28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic heart failure, n (%)</td>
<td>1344 (12)</td>
<td>139 (49)</td>
<td>1205 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HFrEF, n (%)</td>
<td>447 (4)</td>
<td>53 (19)</td>
<td>394 (4)</td>
<td></td>
</tr>
<tr>
<td>HfmrEF, n (%)</td>
<td>422 (4)</td>
<td>32 (11)</td>
<td>390 (4)</td>
<td></td>
</tr>
<tr>
<td>HfPEF, n (%)</td>
<td>378 (3)</td>
<td>37 (13)</td>
<td>341 (3)</td>
<td></td>
</tr>
<tr>
<td>Unknown EF, n (%)</td>
<td>97 (1)</td>
<td>17 (6)</td>
<td>80 (1)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>1895 (17)</td>
<td>130 (53)</td>
<td>1765 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Valve disease, n (%)</td>
<td>1170 (11)</td>
<td>90 (37)</td>
<td>1080 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of valve replacement, n (%)</td>
<td>398 (4)</td>
<td>27 (11)</td>
<td>371 (4)</td>
<td></td>
</tr>
<tr>
<td>Moderate/severe valve dysfunction, n (%)</td>
<td>772 (7)</td>
<td>63 (26)</td>
<td>709 (7)</td>
<td></td>
</tr>
<tr>
<td>Stroke/TIA, n (%)</td>
<td>1070 (10)</td>
<td>37 (13)</td>
<td>1033 (9)</td>
<td>0.04</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>1733 (15)</td>
<td>70 (25)</td>
<td>1633 (15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anaemia, n (%)</td>
<td>4728 (47)</td>
<td>186 (72)</td>
<td>4542 (46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic kidney disease, n (%)</td>
<td>2078 (19)</td>
<td>100 (35)</td>
<td>1978 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic myocardial infarction, n (%)</td>
<td>4345 (39)</td>
<td>200 (76)</td>
<td>4145 (41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urgent/emergency surgery, n (%)</td>
<td>3108 (28)</td>
<td>139 (49)</td>
<td>2969 (27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Revised cardiac risk index, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>I</td>
<td>4485 (40)</td>
<td>31 (11)</td>
<td>4454 (41)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>3812 (34)</td>
<td>79 (28)</td>
<td>3733 (34)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>1928 (17)</td>
<td>93 (33)</td>
<td>1835 (17)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>1037 (9)</td>
<td>80 (28)</td>
<td>957 (9)</td>
<td></td>
</tr>
<tr>
<td>Preoperative medications, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI/ARB/ARNI</td>
<td>4742 (46)</td>
<td>152 (54)</td>
<td>4590 (42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>4484 (40)</td>
<td>175 (62)</td>
<td>4309 (39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ASA</td>
<td>4389 (39)</td>
<td>138 (49)</td>
<td>4251 (39)</td>
<td>0.001</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>561 (5)</td>
<td>20 (7)</td>
<td>541 (5)</td>
<td>0.125</td>
</tr>
<tr>
<td>Statins</td>
<td>5135 (46)</td>
<td>4981 (45)</td>
<td>154 (55)</td>
<td>0.003</td>
</tr>
<tr>
<td>Laboratory assessment, median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine mg/dl</td>
<td>0.94 (0.7–1.2)</td>
<td>1.17 (0.9–1.6)</td>
<td>0.94 (0.8–1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haemoglobin g/dl</td>
<td>12.7 (11–14)</td>
<td>10.8 (9–13)</td>
<td>12.7 (11–14)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; ASA, aspirin; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; HfmrEF, heart failure with mildly reduced ejection fraction; HfPEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IQR, interquartile range; pAHF, postoperative acute heart failure; TIA, transient ischaemic attack.

* 3 = 10.371.
* 3 = 11 148.
* 3 = 10 021.
* 3 = 10 320.
* 3 = 11 257.
* 3 = 11 256.
* 3 = 9973.

patients (11.5%) died within 1 year. Mortality was substantially higher in patients with pAHF versus patients without pAHF (44% vs. 11%; HR 5.49 [95% CI 4.5–6.8], p < 0.001; Figure 2A). After adjusting for confounders, pAHF remained an independent predictor of 1-year mortality (adjusted HR [aHR] 1.66 [95% CI 1.3–2.2], p < 0.001; Table 3). Overall, around 50% of deaths occurred in the first 5 days after the diagnosis of pAHF (online supplementary Figure S3). The Kaplan–Meier curves diverged continuously following the initial peak with patients with pAHF showing a significantly increased risk of death within 120 days of the event, in comparison to patients without pAHF (online supplementary Figure S4). In the subgroup analysis, patients with chronic HF developing pAHF had the highest mortality at 1 year (52%), followed by patients with de novo pAHF (36%) (Figure 3, online supplementary Table S6). Patients with de novo pAHF had higher 1-year mortality than patients with chronic HF (35.6% vs. 24%; HR 1.69 [95% CI 1.22–2.35], p = 0.02;
Figure 1 Characterization of patients with postoperative acute heart failure. Classification according to the European Society of Cardiology guidelines was possible in 219 cases with available left ventricular ejection fraction (after surgery or, if unavailable, before surgery). HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with preserved ejection fraction; pAHF, postoperative acute heart failure.

Table 2 Multivariable logistic regression model for prediction of postoperative acute heart failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>aOR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.064</td>
<td>1.04–1.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.007</td>
<td>0.71–1.43</td>
<td>0.970</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.908</td>
<td>1.41–2.59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.487</td>
<td>1.08–2.04</td>
<td>0.014</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>3.404</td>
<td>2.48–4.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>No insulin</td>
<td>2.018</td>
<td>1.42–2.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin</td>
<td>2.343</td>
<td>1.61–3.42</td>
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<tr>
<td>COPD</td>
<td>1.845</td>
<td>1.34–2.55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>0.813</td>
<td>0.52–1.27</td>
<td>0.359</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>1.495</td>
<td>1.10–2.03</td>
<td>0.010</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>0.993</td>
<td>0.73–1.36</td>
<td>0.965</td>
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<td>Anaemia</td>
<td>1.614</td>
<td>1.16–2.25</td>
<td>0.005</td>
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<tr>
<td>Urgent/emergency surgery</td>
<td>2.003</td>
<td>1.50–2.68</td>
<td>&lt;0.001</td>
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</table>

aOR, adjusted odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; pAHF, postoperative acute heart failure; TIA, transient ischaemic attack.

online supplementary Figure S5). According to the clinical presentation of pAHF, in-hospital and 1-year mortality were 16% and 38% in patients classified as ‘acute decompensated HF’, 26% and 43% in patients classified as ‘acute pulmonary oedema’, 25% and 42% in patients classified as ‘isolated right ventricular failure’, and 67% and 89% in patients classified as ‘cardiogenic shock’. Regarding the occurrence of clinically relevant arrhythmias, patients with pAHF with and without arrhythmias had higher 1-year mortality rates, compared with patients without pAHF (HR 4.91 [95% CI 2.8–8.5, p < 0.001] vs. HR 5.59 [95% CI 4.5–7.0, p < 0.001]). Among the 6568 patients who had undergone elective surgeries, mortality rate of patients with pAHF was 37.1% versus 8.8% in patients without pAHF (HR 5.47 [95% CI 4.0–7.6], p < 0.001) and among the 2596 patients who had undergone urgent/emergency surgeries, mortality rate of patients with pAHF was 49.2% versus 15.5% in patients without pAHF (HR 4.26 [95% CI 3.2–5.6], p < 0.001).

Among 8306 patients eligible for the secondary analysis of readmission for AHF within 1 year, 241 patients (2.9%) were readmitted due to AHF within 1 year. Readmission for AHF was much more common in patients with pAHF versus those without pAHF (15.3% vs. 2.6%; HR 9.1 [95% CI 6.1–13.4], p < 0.001; Figure 2B). After adjusting for confounders, pAHF remained an independent predictor for readmission for AHF within 1 year (aHR 2.33 [95% CI 1.5–3.7], p < 0.001; online supplementary Table S7). In the subgroup analysis, patients with chronic HF developing pAHF had the highest readmission rates due to AHF within 1 year (21%), whereas patients of the de novo pAHF group had similar rates to those of the chronic HF group without pAHF (Figure 3B). Patients with de novo pAHF had similar readmission rates than patients with chronic HF (10% vs. 11.1%; HR 1.05 [95% CI 0.55–2.0], p = 0.895; online supplementary Figure S6).

External validation
The flowchart of patient inclusion is shown in online supplementary Figure S7. Among 1250 patients, pAHF developed in 30 patients...
Figure 2 Cumulative 1-year mortality (A) and readmission due to acute heart failure (B) after non-cardiac surgery in patients with and without postoperative acute heart failure. AHF, acute heart failure; aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; pAHF, postoperative acute heart failure.

Table 3 Multivariable Cox logistic regression model for prediction of mortality within 1 year

<table>
<thead>
<tr>
<th></th>
<th>aHR</th>
<th>95% CI</th>
<th>p-value</th>
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<tr>
<td>pAHF</td>
<td>1.657</td>
<td>1.28–2.15</td>
<td>&lt;0.001</td>
</tr>
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<td>Age</td>
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<td>1.04–1.06</td>
<td>&lt;0.001</td>
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<td>Chronic heart failure</td>
<td>1.211</td>
<td>0.99–1.48</td>
<td>0.058</td>
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<td>Atrial fibrillation</td>
<td>1.501</td>
<td>1.29–1.75</td>
<td>&lt;0.001</td>
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<td>COPD</td>
<td>1.450</td>
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<td>&lt;0.001</td>
</tr>
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<td>Peripheral artery disease</td>
<td>1.201</td>
<td>1.03–1.40</td>
<td>0.021</td>
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<td>RCRI &gt;II</td>
<td>1.716</td>
<td>1.46–2.03</td>
<td>&lt;0.001</td>
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<td>Urgent/emergency surgery</td>
<td>1.690</td>
<td>1.47–1.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postoperative pneumonia</td>
<td>1.904</td>
<td>1.48–2.46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postoperative sepsis</td>
<td>4.066</td>
<td>3.19–5.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postoperative stroke</td>
<td>2.422</td>
<td>1.47–3.98</td>
<td>&lt;0.001</td>
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</tbody>
</table>

aHR, adjusted hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; pAHF, postoperative acute heart failure; RCRI, Revised Cardiac Risk Index.

resulting in an incidence of 2.4% (95% CI 1.6–3.3%). Patients developing pAHF were older, more often had known cardiovascular disorders as well as non-cardiovascular comorbidities versus patients not developing pAHF (online supplementary Table S8). A total of 40% of pAHF cases occurred in the first 3 days after surgery (online supplementary Figure S8). A total of 67% of pAHF cases occurred in patients without known HF (de novo pAHF), and 33% in patients with chronic HF. A total of 103 patients (8.2%) died within 1 year. Mortality was substantially higher in patients with pAHF versus patients without pAHF (20.0% vs. 8.0%; HR 2.90 [95% CI 1.27–6.63], p = 0.008; online supplementary Figure S9).

Discussion

This large multicentre cohort study including high-risk patients using central adjudication was performed to evaluate the incidence, phenotypes, determinants, and outcomes of pAHF following non-cardiac surgery. We report seven major findings.

First, the incidence of pAHF was 2.5%, with most episodes occurring on day 2 following surgery. This observation corroborates and extends estimates obtained in prior pilot studies (1.0% to 3.8%).

Second, our data also confirmed the hypothesis raised in previous retrospective studies that patients undergoing orthopaedic, vascular and emergency surgeries had the highest incidence of pAHF. The early peak of pAHF observed could be explained by the timing of most of the detrimental factors contributing to the development of pAHF: intravenous volume loading to counteract the direct cardiodepressant, vasodilating, and blood pressure lowering effect of the anaesthetic agents, bleeding, and the
systemic inflammatory response, as well as increased myocardial oxygen consumption due to the acute stress response, tachycardia, and pain. Additionally, the presence of undiagnosed congestion before surgery could have contributed to these cases, and more detailed search for congestion, for example by measuring preoperative natriuretic peptide values, and initiation of early therapies could play a role in reducing the risk of pAHF. Regarding patients with known chronic HF, the optimization of the HF medications could prevent the occurrence of pAHF.36 The type of anaesthesia did not seem to play a role in the incidence of pAHF, and the incidence of pAHF did not differ between general, regional or combined anaesthesia. Late cases of pAHF may at least in part have been due to changes in medications, such as withdrawal of diuretics, angiotensin-converting enzyme inhibitors (ACEI) or beta-blockers.

Second, about half of the pAHF patients did not have a history of HF (de novo pAHF). Up to now, studies have focused on the prediction and prevention of postoperative mortality in patients with known chronic HF.17,30,37–39 This observation suggests that these efforts should be extended to all patients at high risk for pAHF. Age, CAD, PAD, diabetes, atrial fibrillation, COPD, chronic HF, anaemia and chronic myocardial injury were independent determinants of pAHF. Careful clinical evaluation of patients with these risk factors before surgery, optimizing treatment of baseline diseases, as well as screening for HF could prevent pAHF. As the RCRI showed moderate accuracy to predict pAHF (AUC 0.73), and is routinely obtained for preoperative risk stratification in our institutions and worldwide, it might help physicians also in the early detection of patients at increased risk of pAHF.33,40–43 Additionally the ESC/ESA classification could also be used to identify the patients who might develop pAHF.

Third, HF with preserved ejection fraction (HFpEF) was the dominant phenotype among de novo pAHF (72%), while HF with reduced ejection fraction (HFrEF) was dominant among pAHF in chronic HF (43%). The dominance of HFpEF among patients with de novo pAHF may be mainly explained by two aspects: first, the diagnosis of HFpEF is more challenging than the diagnosis of HFrEF. Therefore, undiagnosed preoperative HFpEF may have been more common than undiagnosed pre-existing HFrEF, and then decompensated perioperatively. Second, HFpEF seems to be even more vulnerable than HFrEF to the perioperative stressors including volume loading and tachycardia. Given recent evidence documenting benefits in outcomes obtained also when treating HF patients with a LVEF >40%,44,45 the detection of pAHF provides an important opportunity for the initiation of disease-modifying treatment for all pAHF phenotypes. The HF with mildly reduced ejection fraction phenotype was observed in both groups of pAHF (de novo and pAHF in chronic HF), and although there is no hard evidence in this specific phenotype, it is very likely that these patients can also benefit from the drugs that already showed benefit in the whole spectrum of HF, as well as close monitoring and optimization of cardiac risk factors.

Fourth, at hospital discharge, only a small subgroup of patients with chronic HFrEF developing pAHF were on appropriate doses of the three disease-modifying drugs proven to reduce mortality.

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and morbidity at the onset of patient enrolment: beta-blockers, ACEI/angiotensin receptor blockers (ARB), and spironolactone/eplernone. Therefore, the postoperative period provides an important opportunity for the initiation or up-titration of disease-modifying treatment in these patients, particularly as two additional classes have meanwhile been shown to provide incremental value even on top of these three drugs (sacubitril/valsartan, sodium–glucose cotransporter 2 inhibitors). As the patients with pAHF had longer length of hospitalization, it seems reasonable to take the opportunity to improve the medical treatment for HF, and to treat the hypervolaemia to prevent the high rates of rehospitalization.

Fifth, the mortality of patients with pAHF was very high, with nearly half of patients developing pAHF dying within 1 year. As pAHF was found to be an independent predictor of mortality, the extreme mortality observed in patients with pAHF should not be exclusively attributed to their high age (mean age 79 years) and cardiovascular and non-cardiovascular comorbidities. There was a concentration of deaths in the first 5 days, with the curves nonetheless diverging continuously following the initial event, highlighting the need for prevention as well as expert management when pAHF occurs, as well as continuous efforts, since we could still show differences between groups between days 31 and 120. This call-to-action is further supported by recent studies reporting a 1-year mortality of 14% to 16% in patients with chronic HF undergoing non-cardiac surgery. In a retrospective database using International Classification of Diseases codes including patients with a HF diagnosis during the hospitalization for non-cardiac surgery, among patients classified as chronic HF, 29% developed pAHF. The in-hospital mortality of patients with de novo AHF was 8%, similar to the mortality of patients with chronic HF developing pAHF. In our long-term prospective study, the 1-year mortality was higher in patients with chronic HF developing pAHF versus patients with de novo pAHF (52% vs. 36%), and both phenotypes of pAHF were independently related to long-term mortality. Among our patients with chronic HF, only 10% developed pAHF.

Sixth, 15% of patients with pAHF were readmitted to hospital due to AHF within 1 year. Patients classified in the group of chronic HF developing pAHF had the highest readmission rates. These rates are in line with the expected readmission rates for patients hospitalized with primary AHF and chronic HF from registries outside the perioperative context.

Seventh, findings were supported in an independent external validation cohort, where 2.4% of patients developed pAHF, 67% of cases developing as de novo AHF, and patients with pAHF having high 1-year mortality. The small differences in the percentage of de novo pAHF (67% vs. 51%), as well as the lower 1-year mortality observed in the external validation cohort (20% vs. 44%) were probably due to the characteristics of the patients included (only elective visceral surgery, whereas in the study cohort a broad range of elective, urgent and emergency surgeries were included).

A significant clinical implication of the present study is that the perioperative period may represent a stress test for patients with subclinical HF. The diagnosis of pAHF represents a red flag for high mortality risk. The creation of a ‘perioperative team’, focused on the care of high-risk patients, including not only surgeons and anaesthesiologists/intensive care specialists but also internal medicine physicians and cardiologists, may help to decrease the complications and mortality of these patients.

The following limitations should be considered when interpreting our findings. First, despite using a very stringent methodology including central adjudication as well as cardiology consultation in patients developing PML, this study may have missed a small number of patients with mild pAHF, and this may have led to an underestimation of its true incidence. Second, this study included patients older than 65 years or older than 45 years with known atherosclerotic disease, who were referred for in-hospital operations. We cannot comment on pAHF in younger patients or patients undergoing ambulatory surgeries. Third, the management of the perioperative medications was not standardized, therefore it could have had an impact on the incidence of pAHF. However, it is still unclear what is the best management of the ACEI/ARB in different populations. The ongoing STOP-or-NOT randomized trial will hopefully bring some important evidence about the management of ACEI/ARB in the perioperative period. Fourth, the amount of loop diuretics prescribed, the amount of fluids given, the blood loss, the diuretics and the impact on the renal function, as well as NT-proBNP concentrations in most patients were not available. Therefore, we can only speculate about the possible triggers and mechanisms of pAHF.

**Conclusion**

Postoperative AHF occurred in about 1 in 40 patients undergoing major non-cardiac surgery, most often on day 2. The presentation of pAHF was de novo in about half of the cases, and was associated with a very high mortality. Given the availability of well-documented disease-modifying treatment for most pAHF phenotypes, interdisciplinary strategies focusing on early detection and treatment of pAHF seem warranted.

**Supplementary Information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Conflict of interest: D.M.G. reports grants from FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo; Brasil) during the conduct of the study; grants from the Swiss Heart Foundation and personal fees from Roche, outside the submitted work. C.P. reports grants from from Roche Diagnostics; grants from University Hospital Basel, during the conduct of the study; other from Roche, outside the submitted work. M.S.C. has received speaker's fees and honoraria from B Braun AB and Edwards Lifesciences outside the submitted work and holds editorial roles with the European Journal of Anaesthesiology. G.L.B. reports grants from University of Basel, during the conduct of the study; other from Roche Diagnostic, outside the submitted work. F.A.M.C. reports personal fees from Bayer, outside the submitted work. C.K. reports grants from Research Fund Kantonsspital Aarau, during the conduct of the study. D.R. reports personal fees from DePuySynthes and AO Foundation, outside the submitted work. S.O. reports grants from SNSF for Swiss-AF cohort study, from University of Basel, during the conduct of the study; other from Roche, outside the submitted work. G.L.B. reports grants from the Swiss Heart Foundation and personal fees from Ameda, outside the submitted work. A.B. reports grants from Roche, personal fees from Abbott, Beckman Coulter, BRAHMS, Ortho Clinical, Quidel, Roche, Siemens, and Sphingotec, as well as speaker/consulting honoraria from Acon, Apen, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Osler, Novartis, Roche, and Sanofi. All other authors have nothing to disclose.

Appendix

Other Basel-PMI Investigators

Hatice Cakal, Mario Grossenbacher, Michael Freese, Pedro Lopez-Ayala, Silvia Maiorano, Samantha Weder, Ketina Arslani, Christoph Kaiser, Qian Maiorano, Silvia Maiorano, Samantha Weder, Ketina Arslani, Christoph Kaiser, Qian Other Basel-PMI Investigators

References

Acute heart failure after non-cardiac surgery


