PerIoperative iNflammatary reSponse assessment In hiGH-risk patienTs undergoing non-cardiac surgery (INSIGHT): study protocol of a prospective non-interventional observational study

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ABSTRACT

Introduction Increased inflammatory processes after non-cardiac surgery are very common. The association between postoperative inflammation and the occurrence of cardiovascular complications after non-cardiac surgery are still not entirely clear. Therefore, we will evaluate the association between postoperative inflammation and the occurrence of major cardiovascular complications in patients at-risk for cardiovascular complications undergoing non-cardiac surgery. We will further evaluate the association of postoperative inflammation and days-at-home within 30 days after surgery (DAH30), the incidence of acute kidney injury, postoperative N-terminal probrain natriuretic peptide (NT-proBNP) concentrations and neurocognitive decline.

Methods and analysis In this multicentre study, we will include 1400 patients at-risk for cardiovascular complications undergoing non-cardiac surgery. Our primary aim is to evaluate the association of postoperative maximum C-reactive protein concentration and the occurrence of a composite of five major cardiovascular complications (myocardial infarction, myocardial injury after non-cardiac surgery, new onset of atrial fibrillation, stroke and death) within 30 days after surgery using a Mann-Whitney-U test as well as a logistic regression model. As our secondary aim, we will evaluate the association of a composite of three inflammatory biomarkers (interleukin 6, procalcitonin and copeptin) on the occurrence of our composite of five cardiovascular complications within 30 days and 1 year after surgery, acute kidney injury, DAH30 and NT-proBNP concentrations using linear or logistic regression models. We will measure inflammatory biomarkers before surgery, and on the first, second, third and fifth postoperative day. We will check medical records and conduct a telephone survey 30 days and 1 year after surgery. We evaluate neurocognitive function, using a Montreal Cognitive Assessment, before and 1 year after surgery.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The INSIGHT study will be adequately powered to evaluate the association between postoperative inflammation and the incidence of cardiovascular complications within 30 days and 1 year after surgery in patients at-risk for cardiovascular complications.
⇒ Secondary outcomes also include the impact of postoperative inflammation on AKI, days-at-home after surgery and cognitive dysfunction.
⇒ A limitation is that we include different types of surgeries with varying durations and magnitude, which might result in some variability regarding inflammatory responses.
⇒ The sample size of 1400 patients and the multicenter design will allow post-hoc analysis of different surgery types.

INTRODUCTION

The number of patients with cardiovascular risk factors undergoing non-cardiac surgery is steadily increasing over the last decade.1 Preoperative risk factors, including age over 75 years, coronary heart disease, atrial fibrillation and many more, are associated with a higher risk of postoperative complications.2-4 Myocardial injury after non-cardiac surgery (MINS) is a major cardiovascular complication and occurs in up to 18% of patients over 45 years of age.5 Moreover, 4% of patients with MINS will die within 30 days after surgery.6 Furthermore, one out of 33 hospitalised...
patients undergoing major non-cardiac surgery developed severe cardiovascular or cerebrovascular complications in the postoperative period. Specifically, atrial fibrillation occurs in at least 3% of patients having non-cardiac surgery. More recently, it has been shown that approximately 1% of patients, who were older than 65 years undergoing elective non-cardiac surgery had an overt stroke and even 7% of patients developed a covert stroke. Furthermore, acute kidney injury (AKI) occurs in 6.8%–8.5% of all major non-cardiac surgeries and even mild postoperative AKI almost triples the odds of developing chronic kidney disease. All these complications can lead to a prolonged hospital stay or an early readmission after discharge.

Systemic inflammation plays an important role in the development and progression of cardiovascular diseases. Long-term elevated C-reactive protein (CRP), interleukin 6 (IL-6) and procalcitonin (PCT) concentrations, caused by chronic inflammation, are strong predictors for cardiovascular events in the non-surgical setting. IL-6, an acute phase protein, is associated with the incidence of coronary heart disease. Furthermore, the glycoprotein PCT, a precursor of calcitonin and mainly expressed in various extrathyroidal neuroendocrine tissues, is not only a strong marker for systemic inflammation specifically during acute bacterial infections, but is also associated with cardiovascular mortality in patients with coronary artery disease. Whereas copeptin, a stable molecule and a cleavage product from the precursor of arginine-vasopressin, is a significant marker for physiological and pathophysiological stress and is also a strong predictor of MINS.

Besides that, inflammatory biomarkers are elevated on several days after surgery, as a response to increased inflammatory processes. This might be mainly caused by surgical trauma, haemodynamic perturbation, hypothermia and excessive fluid shifts. However, most previous studies were performed in the non-surgical setting and the association of perioperative inflammation and the development of cardiovascular complications is still not clarified. Therefore, we test the primary hypothesis that the incidence of a composite of five major cardiovascular complications within 30 days after non-cardiac surgery is significantly higher in patients with increased CRP concentrations as compared with patients without increased CRP concentrations. We further test the secondary hypothesis that increased CRP concentrations on the fifth postoperative day, and maximum IL-6, PCT and copeptin concentrations are associated with cardiovascular complications within 30 days and 1 year after non-cardiac surgery. We further evaluate the association between postoperative inflammation and AKI, days-at-home within 30 days of surgery (DAH30), postoperative N-terminal pro brain natriuretic peptide (NT-proBNP) concentration and neurocognitive decline.

**METHODS**

**Trial design**

We conduct the perioperative inflammatory response assessment in high-risk patients undergoing non-cardiac surgery—the INSIGHT study, a multicentre prospective non-interventional observational study at the Medical University of Vienna and the Medical University of Graz. All members of the INSIGHT study group are listed in the online supplemental file I. We include 1400 patients at-risk for cardiovascular complications undergoing major non-cardiac surgery. The study was approved by the Ethics Committee of the Medical University of Vienna on the 27th of January 2021 and by the Ethics Committee of the Medical University of Graz on the 4th of June 2021. We started patient enrolment in February 2021 at the Medical University of Vienna and in August 2021 at the Medical University of Graz. We are currently planning to involve further studies sites in Europe.

**Patient involvement**

No patient or public involvement.

**Trial population and patient recruitment**

Detailed information of the inclusion and exclusion criteria is shown in table 1. Patients undergoing laparoscopic and open surgery major abdominal procedures as well as major orthopaedic surgery are eligible. Further information about the definition major surgery is available in the online supplemental file II. We obtain written informed consent before enrolment a day before surgery. Based on previous experience, we approximate that a total of 10–15 patients per week will be enrolled. Therefore, we assume a period of 24–36 month to complete data collection.

**Trial outcomes**

Our primary outcome is the association between postoperative maximum CRP concentration, defined as the highest value measured within the first, second and third postoperative days, and the incidence of a composite outcome of five major cardiovascular complications (including myocardial infarction, MINS, atrial fibrillation, stroke and death) within 30 days after non-cardiac surgery. A trial outcome overview is presented in table 2.

Our secondary aim is the association between the CRP concentration measured on the fifth postoperative day and the incidence of our composite outcome of cardiovascular complications. We further evaluate the association of the maximum values of our three inflammatory biomarkers, which include IL-6, PCT and copeptin, on the incidence of our composite of cardiovascular complications, the incidence of AKI and the DAH30 after surgery and 1 year after surgery. DAH30 will be assessed using data from the medical records and telephone follow-up and the exact method of calculation is described in online supplemental file III.

Additionally, we evaluate the association between the maximum values of CRP, IL-6, PCT and copeptin,
Intraoperative data

We record type and duration of surgery and anaesthesia, intraoperative blood pressure as well as the amount of administered norepinephrine and phenylephrine.

Postoperative follow-up

Study personnel obtain study specific blood samples including CRP, NT-proBNP (Roche), high-sensitive Troponin T (high-sensitivity fifth generation Troponin T, Roche), copeptin, IL-6 and PCT on the first, second, third and fifth postoperative days. Additionally, pulse pressure palpation will be used for atrial fibrillation screening, which was shown to be an appropriate method. In case of pulse irregularity, a 12-lead ECG for verification will be performed. Furthermore, we record hospital records and discharge data for cardiovascular outcome assessment.

All study specific laboratory values are performed at the Department for Laboratory Medicine of the Medical University of Vienna and the Clinical Institute of Medical and Chemical Laboratory Diagnostics of the Medical University of Graz, respectively.

30 days and 1 year follow-up

We contact all patients 30 days and 1 year after surgery via telephone to evaluate the DAH and the following:

Table 1 Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Eligibility (all below)</th>
<th>Inclusion (at least one of below)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery planned for more than 2 hours</td>
<td>NT-proBNP≥200 ng/L</td>
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<tr>
<td>45 years of age</td>
<td>History of stroke</td>
</tr>
<tr>
<td>Proven written informed consent</td>
<td>Diabetes or currently taking antidiabetic drug</td>
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<tr>
<td>≥1 of the inclusion criteria</td>
<td>History of PAD</td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Current smoking or cessation of smoking within 2 years</td>
<td>History of hypertension</td>
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<tr>
<td>75 years or older</td>
<td>History of CIBD</td>
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<tr>
<td>Hyperlipidaemia</td>
<td>CIBD (chronic inflammatory bowel disease)</td>
</tr>
<tr>
<td>Exclusion (none of below)</td>
<td>CIBD, chronic inflammatory bowel diseases; ICU, intensive care unit; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PAD, peripheral artery disease; SIRS, systemic inflammatory response syndrome; TIA, transient ischaemic attack.</td>
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</table>

<table>
<thead>
<tr>
<th>Table 2 Outcomes</th>
<th>Inflammatory parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Composite of cardiovascular events (myocardial infarction, MINS, atrial fibrillation, stroke and death)</td>
</tr>
<tr>
<td>Secondary</td>
<td>Composite outcome of cardiovascular events (myocardial infarction, MINS, atrial fibrillation, stroke and death)</td>
</tr>
<tr>
<td>AKI</td>
<td>Maximum value of CRP, IL-6, PCT and copeptin (first five postoperative days)</td>
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<tr>
<td>Heart failure</td>
<td>Maximum value of CRP, IL-6, PCT and copeptin (first five postoperative days)</td>
</tr>
<tr>
<td>30 days at home</td>
<td>Maximum value of CRP, IL-6, PCT and copeptin (first five postoperative days)</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>Maximum value of CRP, IL-6, PCT and copeptin (first five postoperative days)</td>
</tr>
<tr>
<td>AKI, acute kidney injury; CRP, C-reactive protein; IL-6, interleukin 6; MINS, myocardial injury after non-cardiac surgery; PCT, procalcitonin.</td>
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</tbody>
</table>

Demographic data

We record patient characteristics data including age, sex, body mass index, gender and American Society of Anesthesiologists (ASA) physical status. We record social history including tobacco use, long-term medication and type of surgery. We record preoperative laboratory values as well as cardiovascular comorbidities. Detailed information about the assessment of comorbidities is presented in the online supplemental file V.
complications: myocardial infarction, new onset of cardiac arrhythmias, stroke, and death.

**Statistical considerations**

**Data analysis**

Baseline characteristics such as age, sex, ASA physical status, tobacco use, comorbidities, long-term medication and type of surgery, as well CRP, IL-6, PCT, copeptin and NT-proBNP will first be analysed descriptively. Descriptive statistics will be calculated overall and separately for the two groups (patients with and without major cardiovascular complications). For normal distributed continuous variables, we calculate mean and SD. For non-normal distributed continuous variables, we calculate median, first, third quartile, minimum and maximum.

The primary hypothesis, the association between maximum CRP (over the first 3 days after surgery) and the composite outcome (myocardial infarction, MINS, atrial fibrillation, stroke or death), will be first tested using a Wilcoxon-Mann-Whitney-U test. To account for possible confounding factors (eg, age, sex, ASA status or comorbidities), a logistic regression model with stepwise selection for major cardiovascular complications as target variable will be performed. The significance level for the primary hypothesis is set to 0.05. No correction for multiplicity will be performed. P values of secondary hypotheses will therefore be interpreted in an exploratory way only.

The association between the CRP on day 5, IL-6, PCT and copeptin (maximum over the first 3 days and on the fifth day) and our composite outcome will be analysed using Mann-Whitney-U-tests as well as logistic regression models. Missing values will be handled similar to the statistical analyses of the primary aim.

To evaluate the association of perioperative inflammation (CRP, IL-6, PCT and copeptin) on the occurrence of postoperative AKI, Mann-Whitney-U tests (comparing patients with and without AKI), as well as logistic regression models with stepwise selection for acute kidney injury as target variable also accounting for possible

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**Table 3** Timetable

<table>
<thead>
<tr>
<th>Time</th>
<th>Preoperative visit</th>
<th>Before induction</th>
<th>POD1</th>
<th>POD2</th>
<th>POD3</th>
<th>POD5</th>
<th>Follow-up 30-day</th>
<th>Follow-up 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolment</td>
<td></td>
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<tr>
<td>Eligibility screening</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Patient history</td>
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<td>X</td>
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<tr>
<td>Informed consent</td>
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<tr>
<td>MoCA testing</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Assessment</td>
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<tr>
<td>Composite outcome evaluation</td>
<td>(detailed information provided in online supplemental file IV)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pulse palpation (to detect pulse irregularity) (ECG confirmation by positive pulse irregularity)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory measurements: CRP, IL-6, PCT, Creatinine, high sensitive-Troponin T, NT-proBNP</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Follow-up period

| Postoperative complications via phone follow-up | X | X |

CRP, C-reactive protein; IL-6, interleukin-6; MoCA, Montreal Cognitive Assessment; NTproBNP, N-terminal probrain natriuretic peptide; PCT, procalcitonin; POD, postoperative day.
confounding factors such as, for example, age, sex, ASA status or comorbidities will be performed.

To evaluate the association between perioperative inflammation (CRP, IL-6, PCT and copeptin) and the number of days patients spend at DAH_{30} due to the potentially left skew distribution with a peak at zero,^{30} Spearman correlation coefficients, as well as a median regression model for DAH_{30} as target variable also accounting for possible confounding factors such as, for example, age, sex, ASA status or comorbidities will be performed. Furthermore, as sensitivity analyses, we will use a cut-off of 20 days of DAH_{30} to construct a binary outcome. The cut-off fixed with 20 based on the distribution shown in reference.^{30} The association between perioperative inflammation (CRP, IL-6, PCT and copeptin) and the occurrence of DAH_{30}<20 days, Mann-Whitney-U tests (comparing patients with and without DAH_{30}<20 days), as well as logistic regression models with stepwise selection for the binary outcome DAH_{30}<20 days as target variable also accounting for possible confounding factors such as, for example, age, sex, ASA status or comorbidities will be performed.

To evaluate the incidence of MoCA decline of more than two points from baseline between patients with increased postoperative inflammation and without will be performed using a Fisher Exact-test.

### Sample size

Based on pilot data from our previous investigations,^{31} an average maximum postoperative CRP value of 11.6±8.5 mg/dL was assumed for patients with postoperative cardiovascular complications—compared with an average value of 10.0±8.5 mg/dL for patients without. The complication rate was assumed to be 22.5%. Due to the possible skew distribution of the maximum CRP value, for the sample size calculation, a Mann-Whitney U-test with two-sided significance level of 0.05 was used. Under the described assumptions, 1334 patients in total are needed to achieve 80% power to detect the described difference between groups. Assuming a drop-out rate of about 5%, the sample size of the study was set to 1400.

### Data management and safety

All hard-copy forms, such as case report forms, source data and informed consents will be stored in locked rooms within a secured area which is only accessible by study personnel involved in this study. For electronic data management, we will use the CLINCASE software V.2.7.0.12 (Quadratek, Berlin, Germany). Data storage, back up and hosting of the CLINCASE software will be provided by the IT Systems and Communications—IT-4Science team (Medical University of Vienna). Access data are strictly controlled and will only be provided to the Sponsor (Medical University of Vienna), the study investigators and the ethics commission. All entries and changes in CLINCASE will be tracked.

Data from the Medical University of Vienna will be stored after publishing of the study and all of the substudies by Iron Mountain Austrian Archivierungs GmbH (Gewerbeparkstrasse e3, 2282 Markgrafneusiedl, Austria) for a period of not less than 25 years in accordance with the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by national laws. Data from the Medical University of Graz will be stored after publishing of the study and all substudies at the Medical University of Graz for a period of not less than 25 years in accordance with the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by national laws.

### Ethical considerations

This study is conducted in full conformance with the principles of the ‘Declaration of Helsinki’. The protocol and all related documents provided to the subject were submitted to and approved by the local ethics committees.

### Quality assurance

To ensure sufficient data quality and consistency in trial procedures, all research personnel will be trained before. Additionally, a detailed step-by-step trial Manual of Operations will be available.

### Dissemination

We plan to publish the results in a peer-reviewed journal.

### DISCUSSION

The primary aim of this study is to evaluate the influence of perioperative inflammation on a composite of five postoperative major cardiovascular complications in patients at-risk for cardiovascular complications within 30 days after non-cardiac surgery. Approximately 20% of patients having non-cardiac surgery develop cardiovascular complications within 30 days.\(^6\)\(^7\) It is known that one important trigger factor for perioperative cardiovascular complications is oxygen supply and demand mismatch, caused by for example intraoperative haemodynamic perturbations, surgical trauma, hypothermia and pain. Furthermore, other factors such as perioperative inflammation, hypercoagulability and increased stress response influence postoperative adverse cardiac events. In this context, the underlying aetiology of perioperative cardiovascular complications is multifactorial and complex.\(^32\)

The association between the increased inflammatory processes and the development and progression of cardiovascular complications has been shown in several studies, specifically in the non-surgical setting.\(^33\) For example, an anti-inflammatory treatment with canakinumab in patients with diagnosed myocardial infarction and a high-sensitivity CRP levels of at least 2 mg.L\(^{-1}\) leads to a significant reduction in the incidence of cardiovascular complications.\(^15\) In contrast to the increasing evidence in the non-surgical setting, the role of surgically induced inflammatory response and its association with postoperative cardiovascular complications is still not entirely cleared. However, scant literature about this issue is already published. For example, a distinction in
the preoperative differential count was shown to indicate a higher risk for MINS. In contrast, circulating microRNAs associated with cardiac ischaemia were postoperatively universally elevated and for that reason, were not connected to the incidence of myocardial injury.

Many previous studies evaluated the predictive value of preoperative measured inflammatory biomarkers including CRP, IL-6 and PCT for postoperative surgical complications. It is very well known that patients with diagnosed inflammation associated diseases for example patients with rheumatoid arthritis or inflammatory bowel disease, are at increased risk to develop cardiovascular complications. Specifically, preoperative elevated high-sensitivity CRP is a strong predictor for postoperative cardiovascular complications. Interestingly, we know from previous studies that both inflammatory biomarkers steeply increase within the first 3 days and also cardiac biomarkers, for example, Troponin T and NT-proBNP rise immediately after surgery as well. To evaluate an overall trend, we added day 5 measurements as well. However, our primary outcome includes the first three postoperative days. In fact, the influence of surgically associated inflammation on the development and progression of postoperative cardiovascular complications is still not fully understood and should therefore be answered with this study.

Preoperative NT-proBNP is strongly associated with vascular death and MINS within 30 days after non-cardiac surgery. Even more relevant for our study, increased postoperative NT-proBNP concentrations are independently associated with adverse cardiac events after non-cardiac surgery. Interestingly, NT-proBNP concentrations increase up to fourfold during the first three postoperative days. While increased NT-proBNP might reflect subclinical heart failure, we believe that there might be an important inflammatory component. Specifically, inflammation can lead to volume shifts and could possibly reduce quantitative kidney function in the postoperative period and thus affecting cardiac preload. Otherwise, postoperative myocardial strain due to inflammation, fluid overload or even subclinical heart failure might lead to the significant increase in NT-proBNP concentrations as well. To evaluate postoperative pathophysiologic mechanism regarding inflammation and cardiac function, we assess postoperative NT-proBNP concentrations. We believe that postoperative NT-proBNP concentrations are a better predictor for postoperative complications as supposed to preoperative measurements only.

To take this hypothesis further, we also look at the occurrence of AKI, defined according to the kidney disease improving global outcomes (KDIGO) criteria, after non-cardiac surgery. AKI is associated with increased mortality and prolonged hospitalisation and may also be influenced by inflammatory processes.

In addition to all our laboratory measurements, we will also evaluate the effect of perioperative inflammation on postoperative DAH. There is no data available for the association between perioperative inflammatory kinetic and DAH.

This study has some limitations. We include different types of surgeries with varying durations and magnitude, which might result in some variability regarding inflammatory responses. However, our sample size of 1400 patients will allow posthoc stratification according to type of surgeries. We did not standardise intraoperative haemodynamic and anaesthetic management. It is possible that different types of anaesthesia and pain management will affect inflammatory responses differently. Furthermore, postoperative care is at the discretion of the attending physicians, which might result in varying clinical care.

In summary, the INSIGHT study is adequately powered to show the association between surgical induced inflammation and the occurrence of cardiovascular complications after non-cardiac surgery.

**Trial progress**

Actual protocol: Version 2.0, 8 June 2021. Recruitment started in February 2021 at the Medical University of Vienna and in August 2021 at the Medical University of Graz.

By 4 April 2023, we have enrolled 664 patients.

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**Contributors** Author's contributions are provided in the manuscript: The authors confirm contribution to the paper as follows: conceptualisation: CR, BK, and EF; methodology: CR and AK; development of formal analysis: AG; writing original draft: AP and CR; review and editing: AT, MEichi, MEmchi, BK and EF; supervision: AK; project administration: CR, AT, AP and MEichl; funding acquisition: CR, AT, AP and MEichl.

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**Competing interests** None declared.

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**REFERENCES**


