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RESEARCH PROTOCOL

# Prevention of contrast-associated acute kidney injury in critically-ill and high-risk preoperative patient: Protocol for a systematic review and network meta-analysis

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## ABSTRACT:

**Introduction:** Limited information exists on preventing contrast-associated acute kidney injury (CA-AKI) in critically-ill patients. Extrapolating preventive strategies from non-critically-ill to critically-ill patients may jeopardize data validity. Therefore, it is imperative to evaluate the efficacy of preventive strategies by consolidating available clinical trial evidence through this systematic review and network meta-analysis (NMA).

**Methods and analysis:** We will conduct a comprehensive search of electronic databases, including PubMed, Embase, and Scopus, from their inception dates, with no language limitations. We will include both randomized trials and non-randomized studies that employ validated measurement tools to investigate the benefits of pharmacological interventions in patients undergoing contrast-enhanced computed tomography (CECT). The primary outcome of interest is the incidence of CA-AKI in medically and surgically critically-ill patients who receive medication prior to undergoing CECT. A pair of reviewers will independently perform risk of bias assessments and evaluate the strength of the evidence. We will employ a two-step approach, consisting of traditional pairwise meta-analysis and NMA. Utilizing a random-effects model, we will pool effect estimates as standardized weighted mean differences and odds ratios (ORs) with corresponding 95% confidence intervals (CIs) for continuous and categorical endpoints, respectively. We will assess both statistical and methodological heterogeneities. Preplanned subgroup analyses and univariate meta-regression will be conducted to quantify potential sources of heterogeneity. Evidence synthesis will be based on the effect size magnitudes, certainty of evidence, and surface under the cumulative ranking curve values.

**Ethics:** Ethical approval is not required because this study is based on existing published data.

**PROSPERO registration number:** CRD42022328974

**Keywords:** Critically-ill, Contrast-associated acute kidney injury, Network meta-analysis

## BACKGROUND

Contrast-associated acute kidney injury (CA-AKI) is acute kidney function deterioration following the administration of an iodinated contrast medium (CM). CM is utilized for diagnostic or for intervention purposes. The American College of Radiology (ACR) Committee on Drugs and Contrast Media-2016 established the terms contrast-associated acute kidney injury (CA-AKI) and contrast-induced acute kidney injury (CI-AKI) [1]. CA-AKI is defined as a sudden deterioration in renal function occurring within 48 hours after intravenous administration of CM [1]. CI-AKI is a more specific term and defined as a sudden deterioration in renal function caused by the intravascular administration of CM [1]. The Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group-2012 proposed the term "contrast-induced acute kidney injury (CI-AKI)" and the definition as one of the following that occurs after exposure to CM [2]:

1. An absolute increase in serum creatinine (SCr) ≥0.3 mg/dL within 48 hours.

2. An increase in SCr ≥1.5-fold above baseline within 7 days

3. A reduction of urine output ≤ 0.5 mL/kg/hour for at least 6 hours.

CI-AKI is considered a subset of CA-AKI and a more specific entity of acute kidney injury (AKI) led by CM than CA-AKI, however few studies officially distinguished CI-AKI from CA-AKI [1]. According to the various terms of AKI after CM injection in recent studies, we deem that CA-AKI is a comprehensive term using for those definitions.

CA-AKI is ranked as the third most common cause of hospital-acquired AKI and incidence proportion in the general population is approximately 11% [3] that is greater in a specific population such as patients who underwent cardiac procedures and had preexisting chronic kidney disease (CKD) [4,5]. Many studies demonstrated that CA-AKI is associated with an increase in mortality rate, prolongation of hospitalization, sustained reduction in kidney function at 90 days and early or late cardiovascular events, especially after percutaneous intervention (PCI) [6,7]. Accordingly, a single-center study of 787 critically-ill patients showed that CA-AKI was associated with both short- and long-term adverse outcomes. The short-term outcomes included the need for renal replacement therapy (RRT), worsening of kidney function at discharge, a longer length of intensive care unit (ICU) stay, a hospital stay, and mortality at 28-day. And for the long-term outcomes, a greater mortality rate at 60-day, 90-day, and 1-year was found [8].

Early identification for the patients who are at high risk of worsening renal function is being considered. Predictive models were developed to identify high-risk patients in order to receive preventive strategy [9-11]. Currently, there is no specific treatment available for CA-AKI. Therefore, preventive measures play a main role for reducing the incidence and severity of CA-AKI.

The ACR guidelines recommend infusing fluid at a rate of 100 mL/hour for 6 to 12 hours before and 4 to 12 hours after angiography, where intravenous isotonic saline is the most preferred [1]. Meanwhile, the European Society of Cardiology (ESC) guidelines on myocardial revascularization also recommend using 0.9%NSS or sodium bicarbonate solution at a rate of 1 to 1.5 mL/kg/hour for 3-12 hours before and then 6-12 hours after the procedure [12]. As well as sodium bicarbonate, KDIGO-2012 guidelines and ESC guidelines on myocardial revascularization recommend volume expansion in high risk patients for CA-AKI with either 0.9%NSS or sodium bicarbonate solution [2,12]. Sodium bicarbonate infusion is based on the hypothesis that alkalinized urine protects against oxygen free radical injury through a reduced reactive oxygen species (ROS) generation. Several RCTs had shown that intravenous volume expansion with sodium bicarbonate was superior to 0.9% NSS in reducing the risk of CA-AKI [13-15], the conflicting results that no clear benefit of sodium bicarbonate over 0.9%NSS was found [16,17]. The effectiveness of sodium bicarbonate treatment to prevent CA-AKI remains controversial.

**KEY MESSAGE:**

- Pharmacological interventions could possibly reduce the incidence of CA-AKI in critically-ill patients.

Despite the KDIGO- 2012 guidelines recommends N-acetylcysteine (NAC) either with intravenous isotonic crystalloids [2], the role of antioxidant such as N-acetylcysteine and ascorbic acid remain controversial. The landmark study regarding NAC was the Renal Insufficiency Following Contrast Media Administration (REMEDIAL) trial, which was conducted in 326 patients with CKD who underwent coronary and/or peripheral procedures (iliac-femoral arteriography, carotid artery angioplasty, femoral artery angioplasty, and iliac artery angioplasty) [13]. The patients were randomly assigned to three groups including 0.9%NSS plus NAC, sodium bicarbonate infusion plus NAC, or 0.9%NSS plus ascorbic acid plus NAC. The group of patients who received sodium bicarbonate plus NAC seemed to be superior to the other combination in terms of CA-AKI prevention. The particular group of patients who had the most benefit was the patients who had a medium to high risk of CA-AKI according to the Mehran score [13]. Several studies of ascorbic acid also found no statistically significant whether it could reduce the risk of CA-AKI [18-21].

Huber et al. conducted a small prospective RCT in 150 patients who admitted in ICU and received at least 100 mL of contrast medium. All patients were divided into 3 groups receiving 200 mg of theophylline intravenously in 30 minutes before procedure (T group), 600mg of NAC intravenously twice daily on the day before and after contrast exposure (A group), and both agent combined with same regimen (AT group). The incidence of CA-AKI in groups T, A, and AT was 2%, 12%, and 4% respectively. It appeared that group T has a significantly lower incidence

of CA-AKI than in group A (p=0.047) and there was no significant difference in the incidence of CA-AKI between groups A and AT (p=0.148) or between groups T and AT (p=0.53) [22].

Given this consideration, some issues have been questioned in regards to the CA-AKI in critically ill patients. Moreover, most current evidence for CA-AKI was acquired from the general population or the patients with single organ dysfunction, e.g., CKD. However, there is limited information regarding CA-AKI in critically ill patients who are prone to a higher risk for CA-AKI than the general population, since critically ill patients usually have hemodynamic instability and/or multiple organ dysfunction [8]. Accordingly, applying the evidence for CA-AKI from non-critically ill to critically ill patients could potentially invalidate the data. Therefore, we find it necessary to assess the benefits of preventive strategy by summarizing existing evidence from clinical trials in this systematic review and network meta-analysis (NMA).

## OBJECTIVES

The aim of the outlined systematic review and NMA is to assess the benefits of various medication and bicarbonate infusion as compared with normal saline (0.9%NSS) administration in medical and surgical ICU patients who undergo contrast-enhanced computed tomography (CECT). We hypothesize that these interventions may improve outcomes by reducing the incidence of CA-AKI, mortality rate, need for RRT, and length of stay.

## MATERIALS AND METHODS

### Study design

We will conduct a systematic review and NMA which include data from randomized clinical trials (RCTs) and observational study to assess the preventive protocol of contrast-associated acute kidney injury among participants who undergo contrast enhanced procedure. The key elements of the study design, eligibility criteria, and predefined outcomes based on the population, intervention, comparison, outcome, timing, and setting framework are described in table 1. This study will be performed in accordance with the recommendations of the Cochrane Collaboration Handbook for Systematic Reviews of Interventions V.6.3 [23], the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement [24] and the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach [25].

**Table 1.** The PICOTS format: study inclusion/exclusion criteria.

| Study elements | Criteria for inclusion | Criteria for exclusion |
|---|---|---|
| Populations | • Age ≥ 18 years<br>• Critically-ill patients including medical and surgical ICUs who undergoing CECT | • Age < 18 years<br>• Critically-ill patients who undergo PCI<br>• Patients who developed AKI before CECT<br>• End-stage renal disease patients with/without renal replacement therapy<br>• History of intravascular contrast agent administration in 5 days<br>• Pregnancy |
| Interventions | Any type of pharmacological treatment (ie, normal saline, sodium bicarbonate, N-acetylcysteine, ascorbic acid, theophylline and any medications) | Non-pharmacological studies |
| Comparators | Placebo or 0.9%NSS | Studies without control groups |
| Outcomes | **Primary outcome**<br>• Incidence of contrast-associated acute kidney in medical and surgical critically-ill patients who undergo CECT after receiving medication<br>**Secondary outcomes**<br>• Mortality<br>• Hospital length of stay<br>• Need for RRT<br>• Patient's safety: all adverse events | Studies not providing data to calculate the effect estimates of the outcome of interest |
| Timing | An extensive search strategy from the inception of bibliographical databases forward to assure all published literature will be identified | No restrictions were imposed on timing of start date |
| Setting | • RCTs (include quasi-randomized control trials)<br>• Non-RCTs (observational studies) | • Case–control, cross-sectional studies,N-of-one,case series/case reports and pharmacokinetic/pharmacodynamics studies<br>• Reports not involving primary data including narrative review, systematic review, meta-analysis, news items, consensus statement,guidelines and opinion/editorials |

### Study registration

This review protocol will be prepared according to PRISMA-P statement [24] and the review has been registered at the International Prospective Register of Systematic Reviews (PROSPERO) on 10.05.2022 (www.crd.york.ac.uk/prospero; registration number: CRD42022328974).

## Search methods for identification of studies

### Electronic searches

In collaboration with a proficient medical librarian, we will execute a rigorous systematic search of pertinent evidence by harnessing the capabilities of electronic biomedical databases, which include Embase, Pubmed, and SCORPUS. Our search strategy will be thoughtfully curated, encompassing a combination of primary keywords and medical subject headings specifically centered on CA-AKI, denoting contrast-induced nephropathy or contrast-induced acute kidney injury. We have thoughtfully detailed the pre-established search strategy, alongside the preliminary outcomes of these initial searches for each database, within the confines of Appendix S1.

### Searching other resources

In addition, we will manually search reference lists of included studies and other relevant reviews to identify possible eligible trials. An updated search will be performed before formal analyses and dissemination.

## Data collection and analysis

### Selection of studies

Two authors will independently screen titles and abstract of the trials. Those deemed as relevant will be assessed in full text for eligibility by two authors independently. The full text of potentially relevant articles will be reviewed against the study selection criteria to obtain the final set of included studies. They will be blinded to each other's decisions. The disagreement of judgements will be discussed, if not reach a consensus, the decision will be made by the third reviewer.

### Data extraction and management

In the data extraction process, two independent reviewers will follow a standardized approach, using an electronic extraction form. This meticulous procedure will encompass comprehensive data elements from each study.

Initially, we will collect key information about the study, including the names of the primary and corresponding authors, the study year, location, setting, study design type, and details of the study population, including inclusion and exclusion criteria. Additionally, we will record the size of each treatment group and the duration of the follow-up period.

Subsequently, we will gather participant characteristics and potential effect modifiers, such as the age of study participants (mean, median, or specified age groups), the proportion of male participants, race/ethnicity, underlying diseases, laboratory markers like creatinine and estimated glomerular filtration rate (eGFR), and other medications used.

Furthermore, we will document details of pharmacological interventions and comparison groups, including specific treatment comparisons, dosage of pre-medication protocols, route of administration, and duration of interventions.

Lastly, we will record predefined outcomes of interest, both primary and additional, with a focus on the measurement methods used.

The collected data will undergo a thorough review by two authors to ensure accuracy and consistency. Any discrepancies during data extraction will be resolved through group discussions.

In cases where studies have missing data on outcomes of interest, we will attempt to contact the corresponding author via email. If there is no response within two weeks, a second attempt will be made. If no response is received after the second attempt, we will classify the data as missing or impute it based on data quality.

For numerical endpoints, such as score changes from baseline, we will calculate the mean and standard deviation (SD). If SD values are missing and cannot be obtained from the corresponding author, we will impute the SD following methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions [23].

For binary endpoints, treatment arms with zero events will be adjusted with a value of 0.5 for continuity correction. This ensures proper statistical treatment and data integrity.

### Assessment of risk of bias in included studies

The assessment of the quality of selected Randomized Controlled Trials (RCTs) will be conducted independently by two authors using the Cochrane Risk of Bias version 2 assessment tool (RoB 2) [26]. The RoB 2 tool scrutinizes potential biases across five domains in RCTs, including biases related to the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and bias in the selection of reported results. Each study will be classified as having low risk, high risk, or presenting some concerns regarding bias.

For non-randomized studies, we will employ the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool, consisting of seven domains. These domains encompass biases arising from confounding factors, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results[27]. The ROBINS-I assessments will be categorized as low risk, moderate risk, serious risk, critical risk, or insufficient information. In the event of any disagreements during the assessment process, resolution will be achieved through consultation with a third author.

### Approach to evidence synthesis

Prior to commencing the quantitative synthesis, a preliminary qualitative synthesis will be conducted in adherence to the guidelines outlined in the PRISMA extension statement for systematic reviews incorporating Network Meta-Analysis (NMA) of healthcare interventions[28].

Considering the inclusion of data derived from both Randomized Controlled Trials (RCTs) and non-randomized studies within this NMA, concerns pertaining to data heterogeneity and inconsistency emerge as salient considerations. To address these concerns comprehensively, we will employ tabulation techniques to meticulously scrutinize the attributes of all encompassed studies, thereby facilitating the assessment of both clinical and methodological heterogeneity inherent to each pairwise comparison. Furthermore, we will rigorously scrutinize the transitivity assumption, ensuring the comparability of between-treatment comparisons, and conduct a thorough evaluation of the distribution of participant and study characteristics across the entire spectrum of included studies. Studies failing to meet our stipulated criteria will be subjected to exclusion [23].

The quantitative data synthesis will entail a two-fold approach, encompassing traditional pairwise meta-analysis and NMA. Initially, a traditional pairwise meta-analysis will be conducted for each pairwise treatment comparison, irrespective of heterogeneity, through the application of a random-effects model to derive preliminary pooled treatment effect estimates . The aggregation of continuous endpoints shall be achieved using Standardized Weighted Mean Differences (SMDs), while categorical endpoints will be appraised via Odds Ratios (ORs). Furthermore, to account for the anticipated range of the true treatment effect, we will estimate 95% prediction intervals. Statistical heterogeneity will be rigorously evaluated employing the Cochran Q test, with significance considered at a threshold below 0.10. [29,30] We will evaluate the degree of inconsistency using I2 statistics and tau2 statistics. Potential publication bias or the presence of small study effects will be visually assessed with funnel plots and statistically tested using Begg's and Egger's tests, with a significance level of less than 0.10. Moreover, we will analyze potential small study effects using comparison-adjusted funnel plot symmetry. The evaluation of publication bias will be conducted for pairwise comparisons that include 10 or more trials[31]. Next, we will proceed with Network Meta-Analysis (NMA) to estimate the comparative efficacy of available pharmacological interventions for each outcome of interest. This will be done using a frequentist approach with restricted maximum likelihood estimation. The following steps will be taken in this NMA: we will create a network plot to assess the patterns of connected nodes, followed by the construction of NMA multivariate models using a consistency model. We will perform tests for inconsistency using the global test or Cochran's Q statistics, loop inconsistency, and node-splitting approach. The results of both the consistency and inconsistency models will then be compared. Since there is no clear consensus on the best method to address inconsistency, additional sensitivity analyses will be conducted. These methods may involve removing network portions with inconsistency, splitting nodes in the network, or utilizing study-level or individual-level covariates to explain the etiology of inconsistency [32].

Following this, we will present the comparative treatment efficacy through the presentation of forest plots and league tables. Furthermore, we will employ the Surface Under the Cumulative Ranking Curve (SUCRA) to methodically rank the pharmacological interventions within the interconnected network. Visual representation of the predicted probability of treatment superiority between interventions will be achieved through the use of rankograms. In instances where more than half of the acceptability endpoints are accessible for treatment pair analysis, we will conduct a hierarchical cluster rank analysis, categorizing treatment options based on SUCRA values in respect to efficacy and acceptability outcomes. Lastly, comparison-adjusted funnel plots will be meticulously crafted to assess the presence of publication bias [33].

Pooled estimates for continuous endpoints shall be communicated as Standardized Mean Differences (SMDs) or Weighted Mean Differences, while categorical endpoints shall be explicated via Odds Ratios (ORs). We will consistently calculate and present 95% prediction intervals for all pooled estimates [34] . Predefined subgroup analyses will scrutinize shifts in comparative treatment effects across distinct strata of the following effect modifiers:

1. Participant characteristics, encompassing age (Age < 65 vs. Age ≥ 65) [35], intensive care unit (surgical ICU patients vs. medical ICU patients), presence of anemia, congestive heart failure, diabetes mellitus, and exposure to nephrotoxic agents.

2. Study characteristics, including the duration of treatment follow-up, study quality as determined by risk of bias assessment (categorized as low, indicative of some concerns, or high), and geographical regions.

All statistical analyses shall be executed using Stata V.17 software (StataCorp, College Station, Texas, USA). Results exhibiting a two-tailed p-value below 0.05 shall be accorded statistical significance.

## Assessing the quality of the evidence

Two independent reviewers will evaluate the level of confidence and the quality of evidence associated with each outcome. They will employ a combination of the modified confidence assessment in Network Meta-Analysis (NMA) method and the Grading of Recommended Assessment, Development, and Evaluation approach [25,36]. The quality of evidence may be adjusted based on factors such as the risk of bias, imprecision, inconsistency, and indirectness in the research findings. The evidence will be categorized into four tiers: very low, low, moderate, and high quality. In cases of disagreement, a team discussion will be conducted to reach a consensus on the certainty of evidence grading.

To establish treatment network effect estimates in the context of preventive protocols, we will adopt a comprehensive approach, taking into account both clinical and methodological considerations. We will arrive at an evidence-based conclusion by synthesizing all finalized data on treatment effect estimates, considering factors such as the magnitude of effect size, prediction intervals, SUCRA values, and the certainty of evidence.

The estimated treatment effect magnitude will be interpreted as follows: very small effect (SMDs less than 0.2; ORs less than 1.68), small effect (SMDs between 0.2 and 0.4; ORs between 1.68 and 3.46), medium effect

(SMDs between 0.5 and 0.7; ORs between 3.47 and 6.71), or large effect (SMDs 0.8 or greater; ORs 6.72 or greater) [37-39]. In summary, pharmacological interventions will be categorized as either trivial (indicating no significant difference from placebo, standard treatment, or usual care), small, moderate, or large effects. This categorization will facilitate clinical interpretation and help rank the clinical evidence of the findings.[39]

## ETHICS AND DISSEMINATION

This systematic review did not have direct involvement of human subjects. Therefore, ethical approval is not required. The Ethical Committee of the Faculty of Medicine, Chiang Mai University has granted an ethical exemption for this study.

## DISCUSSION

Contrast medium administration in critically-ill patients may lead to CA-AKI. Recently, we have gained better understanding of the pathophysiology and risk factors of CA-AKI. Creating a prediction model to early identify the high risk patients, moreover, there has been increasing in the evidence on CA-AKI prevention. Preventive strategy aims to reduce the incidence of CA-AKI as a result of increase in mortality rate, need for RRT, and length of stay. This network meta-analysis will provide data on the evidence of preventive strategy benefits in critically-ill patients, on which future recommendations may be founded. Strengths of this outlined review will be the first network meta-analysis of CA-AKI prevention in critically-ill patients.

The limitation of these circumstances, our NMA will gather available studies of various designs. We aim to deliver a more comprehensive review that would show an overall comparative efficacy among the currently available pharmacological options. Finally, we hope that the findings from this study will reveal more positive correlations between CA-AKI reduction rate and preventive interventions in critically-ill patients, which might encourage more studies to explore further the combinations of pharmacological therapy and ultimately leading to better knowledge of best practice for the renal protective effects in ICU patients.

## CONFIDENTIALITY

This NMA did not have direct involvement of a private personal data, therefore limiting access to study data to a permissive members was not required.

## ACKNOWLEDGEMENT

None

## SUPPLEMENTARY MATERIALS

None

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## SUPPLEMENTARY FILES

**Appendix S1 Systematic review search strategy: PubMed**

| No. | Search term | Result |
|---|---|---|
| 1 | Contrast induced nephropathy | |
| 2 | Contrast associated acute kidney injury | |
| 3 | Contrast induced acute kidney injury | |
| 4 | (contrast induced nephropathy) OR (contrast associated acute kidney injury) OR (contrast induced acute kidney injury) | |
| 5 | Critically ill | |
| 6 | Intensive care | |
| 7 | (critically ill) OR (intensive care) | |
| 8 | Prophylaxis | |
| 9 | Prevention | |
| 10 | (prophylaxis) OR (prevention) | |
| 11 | No.4 AND No.7 | |
| 12 | No.4 AND No.7 AND No.10 | |

**Appendix S1 Systematic review search strategy: EMBASE**

| # | Search terms | Results |
|---|---|---|
| 1 | Intensive care/ | |
| 2 | Intensive care unit/ | |
| 3 | Critically ill patient/ | |
| 4 | Perioperative/ | |
| 5 | 1 or 2 or 3 or 4 | |
| **Intervention search set (containing terms related to intervention types, intervention areas and study designs)** | | |
| **#** | **Search terms** | **Results** |
| 6 | Prevention/ | |
| 7 | Prophylaxis/ | |
| 8 | 5 or 6 | |
| **Outcome search set (containing terms related to intervention outcomes)** | | |
| **#** | **Search terms** | **Results** |
| 9 | Contrast induced nephropathy/ | |
| 10 | Contrast induced acute kidney injury/ | |
| 11 | Contrast associated acute kidney injury/ | |
| 12 | 8 or 9 or 10/ | |
| **Joint search sets** | | |
| **#** | **Search terms** | **Results** |
| 13 | 5 and 12 | |
| **Search set to exclude animal studies** | | |
| **#** | **Search terms** | **Results** |
| 14 | limit 13 to human | |

**Appendix S1 Systematic review search strategy: SCOPUS**

| | |
|---|---|
| **SCOPUS** | **The following search parameters were used:**<br><br>· **Title, abstract, keywords:** contrast induced nephropathy, contrast induced acute kidney injury, contrast associated acute kidney injury, critically ill patient, intensive care unit, perioperative<br>· **Time:** all years to present<br>· **Document types:** all document types<br>· **Subject areas:** medicine |
| **SCOPUS** | **The following search syntax was used:** TITLE-ABS-KEY ( contrast AND induced AND nephropathy ) OR TITLE-ABS-KEY ( contrast AND induced AND acute AND kidney AND injury ) OR TITLE-ABS-KEY ( contrast AND associated AND acute AND kidney AND injury ) AND TITLE-ABS-KEY ( intensive AND care ) OR TITLE-ABS-KEY ( intensive AND care AND unit ) OR TITLE-ABS-KEY ( critically AND ill AND patient ) OR TITLE-ABS-KEY ( perioperative ) AND ( LIMIT-TO ( SUBJAREA , "MEDI" ) ) |