# A systematic scoping review on the clinical burden of hyperglycaemia in ICU patients

**Aurélie Danel[1], Montserrat Miret [1], Elena Olariu [2], Nicholas Pooley [2], Jean-Charles Preiser [3]**

**1. Nestlé Health Science, Vevey, Switzerland 2 PHMR Ltd, London, United Kingdom 3. Department of Intensive Care, Erasme Hospital, Université libre de Bruxelles, Brussels, Belgium**

## Introduction

Hyperglycaemia frequently occurs in critically ill patients, with studies reporting that almost 75% of intensive care unit (ICU) patients, including diabetics, have blood glucose >110 mg/dl [1]. Hyperglycaemia is associated with complications, prolonged ICU and hospital stay, and increased mortality [2–4].

However, to date, no previous research has systematically reviewed the clinical burden of hyperglycaemia in ICUs in observational studies, which are in general more representative of real-world patients.

## Aim

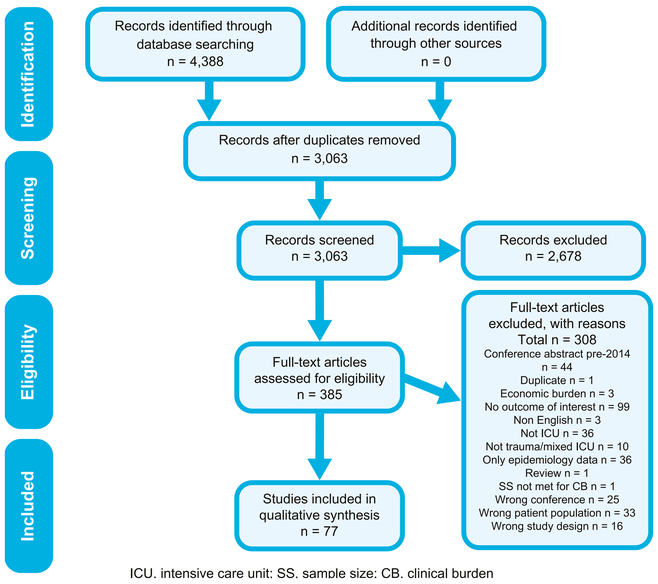
We performed a systematic scoping review to understand the clinical burden of hyperglycaemia in ICU patients and the different methods used to report it in observational studies.

## Methods

We followed the Joanna Briggs methodology guidance to perform a systematic scoping review to identify relevant publications in Medline, Embase, and The Cochrane Library from January 2000 to December 2015. Two reviewers assessed studies for eligibility. Studies were included if they reported on mortality, infections, hospital/ICU length of stay, time on ventilation and ICU-acquired weakness in adult patients (≥18 years) with hyperglycaemia in ICUs. No definition for hyperglycaemia was set *a priori*. Data extraction was performed by one reviewer and checked by another.

## Results

Overall, 4,388 records were retrieved. After deduplication 3,063 titles were screened, 385 full-text articles were reviewed, and 77 studies (1,172,172 patients) were included in the review (Figure 1).




ICU. intensive care unit: SS. sample size: CB. clinical burden

***Figure 1 – PRISMA flow diagram of included studies***

### Study design and methodology

The majority of the included studies (74%) were conducted in either the USA (35 studies) or in Europe (22 studies).

Most of the studies were retrospective (40) and 32 were prospective.

Most of the research available on the clinical burden of hyperglycaemia in ICU was conducted in trauma ICU patients (25 studies) and in mixed ICU patients (28 studies, including 10 conducted exclusively in cardiac ICU patients). Sample sizes varied widely from 28 patients to 779,786 patients.

The most common blood glucose thresholds used to define hyperglycaemia were 200 mg/dl (18 studies), 180 mg/dl (11 studies), 150 mg/dl (11 studies) and 140 mg/dl (9 studies). The range of thresholds varied from 100 mg/dl to 300 mg/dl.

Regarding the method of blood glucose measurement, a high variability was observed across studies. Studies reported having measured either capillary (12 studies), arterial (11 studies), or venous blood glucose (8 studies), using either blood gas analysers, point-of-care glucometers, point-of-care finger sticks or laboratory interfaces. The timing/frequency of measurement was seldom reported in the included studies, with only ten studies reporting having measured blood glucose levels at ICU admission.

The majority of studies (68) reported on mortality. Other outcomes, such as ICU and hospital length of stay and infections were less frequently reported (38, 27 and 23 studies, respectively) (see Figure 2). Studies conducted in trauma and mixed ICU patients most frequently reported on hospital mortality and ICU and hospital length of stay. Infections were more commonly reported in trauma (43.5%) and cardiac ICU patients (17.4%). Mortality was reported together with ICU and hospital length of stay in 14 studies in trauma ICU patients, in four studies in mixed ICU patients and in one study in cardiac ICU patients.

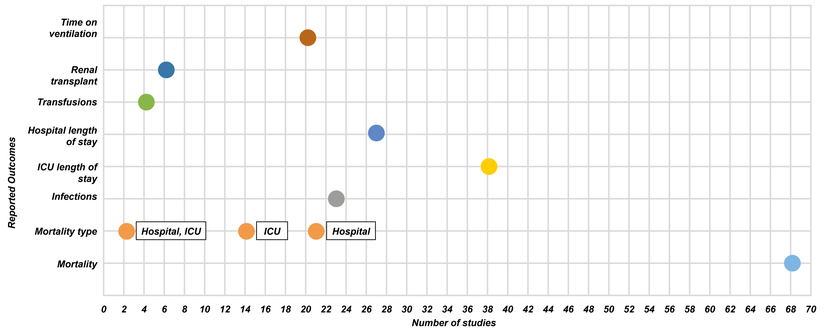



***Figure 2 – Distribution of reported outcomes in observational studies on the clinical burden of hyperglycaemia in intensive care units (ICU)***

### Studies reporting on mortality

Of the studies that reported on mortality, 25 assessed whether hyperglycaemia was an independent risk factor for mortality. Mortality was expressed either as hospital (10 studies) or ICU mortality (3 studies), or as short-term (7 studies) and long-term mortality (3 studies). The type of mortality was not reported in two studies. Most of these studies showed that higher levels of blood glucose were associated with a higher risk for mortality even after adjusting for confounding variables. A similar trend was observed in ICU patients with diabetes: lower levels of blood glucose were associated with a reduced risk of mortality [3,5]. Only three studies assessed the impact of hyperglycaemia on long-term mortality: 20-year mortality [3], five-year mortality [6] and one-year mortality [4] (see Table 1).

***Table 1 – Hyperglycaemia as a risk factor for long-term mortality in ICU patients***

| Author, year | Sample size, n | Risk factor | Mortality type | Outcome (95% CI) |
|---|---|---|---|---|
| **Deckers et al. 2013** [3] | All patients, n=11,324 | Admission BG | 20-year | Mild HG: ORa=1.1 (1.1 – 1.2)<br>Severe HG: ORa=1.6 (1.5 – 1.8) |
| | | | 20-year among 30-day survivors | Mild HG: ORa=1.1 (1.0 – 1.2)<br>Severe HG: ORa=1.4 (1.3 – 1.5) |
| | Diabetic patients, n=68 | | 20-year | Mild HG: ORa=0.88 (0.71 – 1.1)<br>Severe HG: ORa=1.3 (1.1 – 1.5) |
| | | | 20-year among 30-day survivors | Mild HG: ORa=0.83 (0.66 – 1.0)<br>Severe HG: ORa=1.1 (0.89 – 1.3) |
| **Kadri et al. 2006** [4] | Non-diabetic patients, n=1,604 | Admission BG | One-year mortality | Admission glycaemia (v 3 first sextiles)<br>4th sextile OR=1.64 (1.00 – 2.71)<br>5th sextile OR=1.81 (1.14 – 2.87)<br>6th sextile OR=2.29 (1.49 – 3.51) |
| **Mansur et al. 2015** [6] | All patients, mixed diabetic status, n=455 | BG ≥150 mg/dl | 5-year mortality | HR=2.10 (1.30 – 3.39; p=0.0023) |

***BG,** Blood Glucose; **CI,** Confidence Interval; **HG,** Hyperglycaemia; **HR,** Hazard Ratio; **ICU,** Intensive Care Unit; **OR,** Odds Ratio; **ORa,** adjusted Odds Ratio.*

### Studies reporting on infections

Of the studies that reported on infections, only eight assessed whether hyperglycaemia was a risk factor for developing infections during ICU stay [7-14] and five of them [9-12,14] identified it as an independent risk factor for infections. Across these latter studies, hyperglycaemia, as an independent risk factor, was expressed as hyperglycaemic index (ORa=1.8, 95% CI 1.3 – 2.5) [11], as blood glucose levels ≥ 200 mg/dl (p =0.02; no ORs reported) [10], (p =0.007; no ORs reported) [14], or >135 mg/dl (urinary tract infections: ORa=3.3, 95% CI 1.21 – 8.8; pneumonia: ORa=2.8, 95% CI 0.98 – 8.0) [9], or as pattern of glucose control [12].

### Studies reporting on ICU and hospital length of stay

Of the studies that reported on ICU and hospital length of stay, only one assessed whether hyperglycaemic patients had an increased risk for longer ICU and hospital stays [14]. This study showed that glucose was an independent predictor of ICU and hospital length of stay, independent of Injury Severity Score (partial t-test, $p < 0.01$), Revised Trauma Score (partial t-test, $p < 0.01$) and age (partial t-test, p=0.016).

## Conclusions

Hyperglycaemia at admission or acquired in ICU is significantly associated with increased disease severity and considerable burden on healthcare resources.

The available literature on the burden of hyperglycaemia in ICU is highly heterogeneous in the blood glucose thresholds used, in how blood glucose is measured and monitored, and in how outcomes are reported.

Very few studies provide information on therapeutic protocols used, on the time, frequency and method of glucose measurement, or on the type of enteral nutrition patients received.

Improvement in reporting and conduct of observational studies exploring the clinical burden of hyperglycaemia in ICU is imperative to allow better comparability between study results and quantitative analysis of the available data.

## Disclosures

AD and MM are permanent employees of Nestlé Health Science. EO, NP and JCP have received consulting fees from Nestlé Health Science.

Abstract prepared for the Clinical Nutrition Week 2017, conference of the American Society for parenteral and enteral nutrition (ASPEN).

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