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THE DIAGNOSTIC PERFORMANCE OF PLASMA NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN IN DETECTING ACUTE KIDNEY INJURY (AKI) IN ADULT CRITICALLY ILL PATIENTS COMPARED WITH CREATININE IN BLOOD

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ABSTRACT

Background: Acute Kidney Injury (AKI) is prevalent among critical illnesses and related with over 50% death. In current practice the detection of AKI is based on elevation of creatinine ≥ 50% from the baseline (RIFLE/AKIN criteria). Although creatinine in blood is influenced by factors as age and muscles mass. Thus new biomarker was reported to identify AKI in critical ill patients in order to prevent AKI and reduce the mortality by AKI. This was neutrophil gelatinase-assossiated lipocalin (NGAL). **Aim:** To assess the diagnostic performance of plasma NGAL (pNGAL) in detecting AKI in adult critically ill patients without AKI at the Intensive Care Unit (ICU) entry compared with creatinine in blood (serum or plasma). **Method:** Electronic search through Glasgow Caledonian University (GCU) used AMED, CINHAL and Medline databases (EBSCO)**.** The used keywords were: (Critical ill patients or critical illness or critical care) and (NGAL or neutrophil gelatinas-associated lipocalin). The scanning for eligibility was initially throughout the title then reading the abstract to select the articles that met the inclusion criteria. Finally, the studies were assessed for the quality by using Scottish Intercollegiate Guidelines (SIGN) diagnosis checklist. **Results:** The final search's results were thirty two articles**.** Eight out of 32 articles were scanned for eligibility. Only six articles were included. The significant diagnostic performance of pNGAL compared with creatinine in blood in each study was: Constantin et al (2010) $P = 0.956$; Cruz et al (2010) $P = 0.0001$; De Geus et al (2011) $P < 0.001$; Kokkoris et al (2012) $P = 0.001$; Aydogdu et al (2013) $P = 0.44$ and Pickring & Endre (2013) $P = 0.06$. **Conclusion:** pNGAL is a good test to diagnose AKI. Despite that, large multicentre studies are recommended to generalize the findings.

INTRODUCTION

Critical illnesses are admitted to the Intensive Care Unit (ICU) which is a life-threatening and high sensitive unit where the patients require close monitoring and cared by trained staff. The critically ill patients who need special care includes: patients with serious head injury, post-surgical operation procedure, heart attack, patients with imbalance acid- base electrolyte, diabetic mellitus, lung disease, etc. (Brilli et al, 2001). These clinical settings may develop Acute Kidney Injury (AKI) depends on the severity of the disease.

AKI is a status that caused by multiple factors which leads to a sudden decrease in kidney functions. It occurs in different clinical settings with different clinical appearances ranging from acute injury to severe injury leads to complete loss of kidney function. AKI results in a high risk of illness and death (NKF, 2014). There are three main causes of AKI which are: pre-renal like: hypotension, the second cause is intrinsic renal problem as: glomerular disease and the third cause is post-renal like: calculus (Rahman et al, 2012).

AKI is common among critical illnesses. About 20%-50% is the prevalence of AKI in the ICU and over 50% death (Case et al, 2013). Balushi et al (2011) study investigated the occurrence, causes and effect of AKI at Sultan Qaboos University Hospital (SQUH) in Oman and showed that 2.11% was the prevalence of AKI in ICU patients.

AKI is characterized by the build-up of wastes like creatinine, nitrogen and blood urea, and an express decay in the glomerular filtration rate (GFR). Indeed, the occurrence of renal function impairment is within hours to days. AKI has been substituted the Acute Renal Failure (ARF) terminology; because the ARF is concerned only the kidney failure function and fails to describe the varied biochemical, molecular and the structure of the process that characterized AKI syndrome (Devarajan, 2010).

Previously, a research of AKI includes many definitions as 35 different diagnosis of AKI, until 2004 when the Risk, Injury, Failure, Loss and End-stage (RIFLE)

criteria was issued by Acute Dialysis Quality Initiative (ADQI), which used the variations in serum creatinine and urine output from the baseline to define the AKI. Moreover, because of the slight elevation in serum creatinine is not taken by RIFLE criteria, the Acute Kidney Injury Network (AKIN) planned a guideline which is more sensitive for the detection of AKI. The RIFLE/AKIN criteria are illustrated in table 1 (Case et al, 2013). The Kidney Disease Improving Global Outcomes (KDIGO) issued guidelines for acute kidney injury (AKI) in 2012, which based on the RIFLE and the AKIN criteria.

Table 1: The RIFLE/AKIN criteria.

Criteria		Serum creatinine	Urine output
RIFLE	R=Risk	Rise ×1.5 or GFR reduced > 25%	< 0.5 ml/kg/h used for 6 hours
	I=Injury	Rise × 2 or GFR reduced > 50%	< 0.5 ml/kg/h used for 12 hours.
	F=Failure	Rise × 2 or GFR reduced > 70% or serum creatinine > 4mg/dl	< 0.3 ml/kg/h used for 24 hours or anuria for 12 hours.
AKIN	Stage 1	≥ 0.3mgldl or elevate to ≥ 150-200% from the baseline	< 0.5 ml/kg/h used for 6 hours.
	Stage 2	>200-300% from the baseline	< 0.5 ml/kg/h used for 12 hours
	Stage 3	Rise to 300% from the baseline or serum creatinine ≥ 4.0mg/dl with acute elevation of ≥ 0.5mg/dl.	< 0.5 ml/kg/h used for 24 hours or anuria for 12 hours.

In current practice AKI is detected by RIFLE/AKIN criteria. However, serum creatinine is unreliable for detecting AKI because of its limitations that it does not reveal kidney function in acute injury; because creatinine influences by age, sex, medication and muscle mass. Also, it does not elevate until most of renal function has been lost which require several days (Devarajan, 2008). In order to reduce morbidity and mortality because of AKI, a new biomarker has been reported to identify AKI. This was neutrophil gelatinase-associated lipocalin (NGAL) (Kim et al, 2013).

Neutrophil gelatinase-associated lipocalin (NGAL) or lipocalin-2 or *Lcn2 i*s a protein of 25-kDa from lipocalins superfamily. It released by the neutrophils cell. It binds to neutrophil gelatinase. The NGAL is synthesized during the second granules formation at the granulopoiesis early stage which is myelocyte. The normal expression of NGAL (mRNA) found in many tissues like: uterus, liver, salivary gland, prostate, stomach, lungs, colon, bone marrow and kidney (Devarajan, 2010). NGAL is found in the kidney cortical tubules, urine and blood subsequent the ischemic injury and nephrotoxic. It is excreted rapidly by renal tubules in reaction to injury (Malyszko, 2010).

In Oman the AKI diagnosis is based on RIFLE and AKIN criteria (MOH, 2010). There is no protocol to use NGAL to identify AKI. In order to prevent AKI by a good diagnosis and management, this review aimed to critically review the best evidence of the diagnostic performance of plasma NGAL to detect AKI in adult (male and female) critically ill patients without AKI at ICU admission compared with creatinine in blood. The intervention is plasma NGAL, the comparison is creatinine in blood (serum or plasma), the population is adult critically ill patients and the outcome measure is the diagnostic performance of plasma NGAL.

METHOD

To review the best evidence on the performance of plasma neutrophil gelatinase-associated lipocalin (pNGAL) in detecting Acute Renal Injury (AKI) in adult critically ill patients without AKI at the Intensive Care Units (ICU) admission compared with creatinine in blood. Therefore, several databases, e.g. Medline, EBSCO and Science Direct were used to find out the best evidence. In all of these databases, the same articles were found; therefore the relevant articles were taken from EBCO.

- **Criteria for considering evidences for the review**

Type of study

According to the review's topic the search was focused on searching for studies which investigate the two tests and have the same inclusion criteria in order to answer the PICO question.

Population

Critically ill patients who were > 19 years old (adult) male and female were admitted at general, medical, surgical and pulmonary ICUs.

Intervention

Plasma neutrophil gelatinase-associated lipocalin (pNGAL) test measured on entry of ICU, then after 4, 8, 24, 36, 48, 60, 72 hours of admission.

Comparison

Creatinine in blood (serum or plasma) is a gold standard for AKI diagnosis; it was measured at ICUs admission and daily after that.

Outcome measures: To measure the diagnostic performance of pNGAL in detecting AKI in adult critically ill patients without AKI at ICUs admission.

- **Method of search**

Inclusion and exclusion criteria were used to check the eligibility of the studies which will include in this review. Table 2 shows the inclusion and exclusion.

Table 2: The inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Prospective cohort or observational studies about critically ill patients without Acute Kidney Injury (AKI) at Intensive Care Unit (ICU) admission.	Systematic review, meta-analysis and case studies about critically ill patients without AKI at ICU admission.
Critically ill patients admitted in medical, surgical, general, pulmonary ICU.	Critically ill patients admitted in paediatric ICU.
Plasma neutrophil gelatinase-associated lipocalin (pNGAL) to diagnose AKI.	Urinary neutrophil gelatinase-associated lipocalin to diagnose AKI.
Serum or plasma creatinine.	Glomerular Filtration Rate (GFR), urine output.
Adult > 19 years old, male and female.	Paediatric male and female.

Electronic search: The search was conducted by a strategy to find out literatures that answer the review's question. The strategy was carried out through Glasgow Caledonian University (GCU). Three databases which were: AMED, CINAHL and Medline (EBSCO) were used because these databases comprehensive, which include all biomedical, biochemistry and chemistry's literatures. The search was carried on from 14/2/2014 to 20/3/2014 to get the best evidence. The keywords which were used for the population and intervention are shown in table 3.

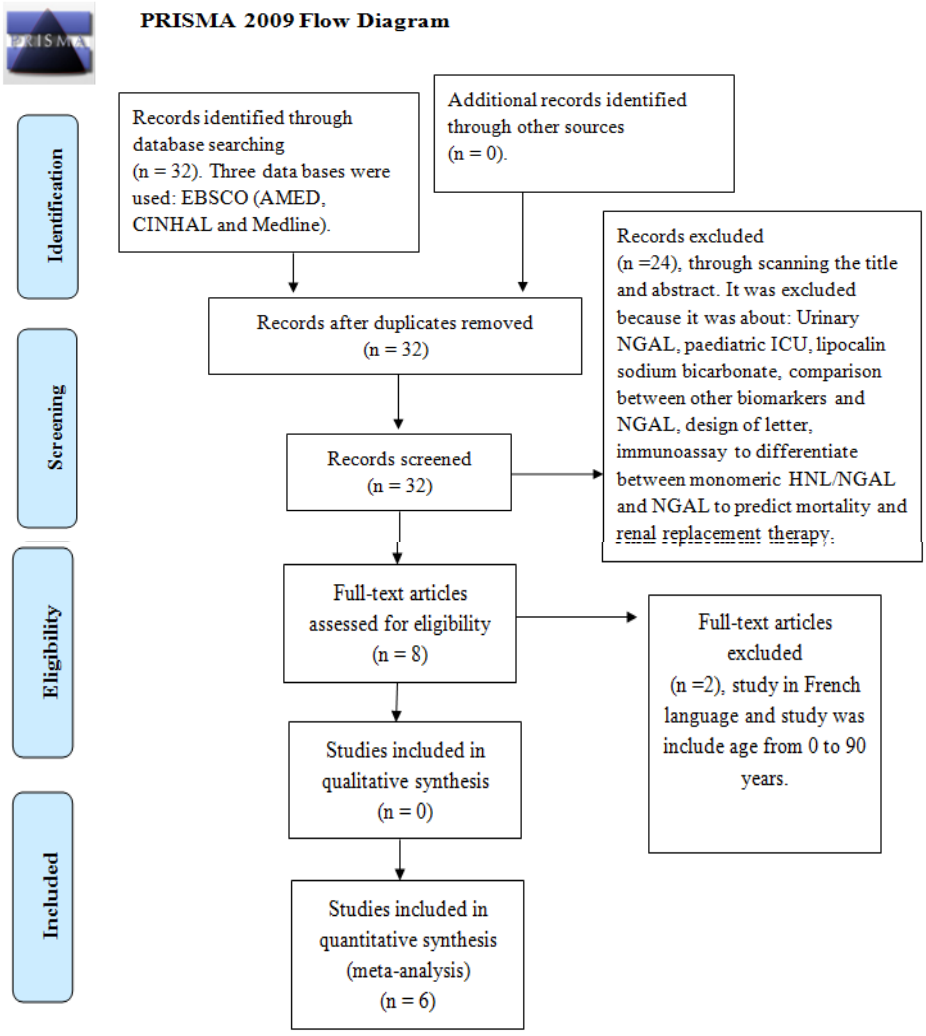
Table 3: The search keywords.

	Keywords
Intervention	NGAL or neutrophil gelatinase-associated lipocalin.
Population	Critical ill patients or critical illness or critical care.

The full text was selected to get free access articles. The publication date was limited to the last 10 years because in 2003 the NGAL was identified as a potential biomarker for AKI (Kim et al, 2013), so the search focused during this period to get the most recent evidence. English language was selected because it is readable. The articles were peer reviewed in order to ensure validity and reliability.

The final search results through the three databases were scanned for the relevant articles throughout the title because it gives an insight into the topic and context. Exclusion of some articles was via the abstract because it contains the summary of the article and gives an overview of the literature. The relevant articles that met the inclusion criteria of the review were scanned throughout the full text because it includes details of the context (appendix 1).

Appendix 1: PRISMA Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097
For more information, visit www.prisma-statement.org.

- **METHOD OF REVIEW**

Study selection

The selection of each article was based on its relevance to the aim of the review and it was restricted to studies (prospective: cohort and observational) that investigate the performance of pNGAL in detecting AKI in adult critically ill patients without AKI at ICUs admission. All relevant articles were not available in full text; therefore it viewed by another link resource.

Appraising the articles

The Scottish Intercollegiate Guidelines Network (SIGN) checklist tool for studies of diagnostic accuracy was used to appraise the quality level of each study. It was used because of its based quality design checklist that explores the differences, limitations and strengths of the study in order to make judgments for the suitability and recommendation for future research (SIGN, 2014) (appendix 2).

Appendix 2: SIGN checklist for studies of diagnostic accuracy.

Study	Participants	1.1	1.2	1.3	1.4	2.1	2.2	2.3	3.1	3.2	3.3	4.1	4.2	4.3	Remarks
Constantin et al (2010)	56	√	×	√	√	√	√	√	√	√	√	√	√	√	Double blind
Cruz et al (2010)	301	√	√	√	√	√	R	√	√	√	√	√	√	√	Technicians were blinded to clinical data and sample source
De Geus et al (2011)	632	√	×	√	√	√	R	√	√	√	√	√	√	√	Technicians were masked to clinical data
Kokkoris et al (2012)	100	√	×	√	√	R	√	√	√	R	√	√	√	√	-
Aydogdu et al (2013)	151	√	√	√	√	R	√	√	√	R	√	√	√	√	-
Pickerning (2013)	276	√	×	√	√	R	R	√	√	R	√	√	√	√	-

√: Yes (met the criteria), ×: No (did not met the criteria), R: Not recorded.

1.1- The included patients suspected to have the target condition.

1.2- The study used control group for the comparison in order to exaggerate diagnosis accuracy.

1.3- The exclusion criteria were clearly described.

1.4- The included patients were matched with the target population of the guideline (demographic feature, co-morbidity).

2.1- The index test was done blindly.

2.2- Threshold (cut-off) was specified at the beginning of the study to avoid reporting bias.

2.3- The index test was described clearly.

3.1- The reference standard classifies the condition correctly.

3.2- The results of reference standard were taken without the information about the index test results.

3.3- The identification of the target illness by reference standard was matched with the target population of the guideline.

4.1- The time between the index test and reference standard is sufficient to ensure that the target illness did not alter among the both tests.

4.2- All of the patients received the same reference standard.

4.3- An explanation for withdrawals was provided.

RESULTS

Thirty two literatures were the final result of the electronic search. Eight out of 32 articles from the three databases were scanned for eligibility throughout the full text. Two out of the eight studies were excluded because one of them was in the French language since the review was based on published articles in English which are readable, while another study was excluded because it includes patients aged from 0 to 90 years old since the inclusion age is > 19 years. Six studies were selected for the review because it met the inclusion criteria, and it was assessed for quality by using SIGN checklist for studies of diagnostic accuracy. According to this all six articles were included (Constantin et al, 2010; Cruz et al, 2010; De Geus et al, 2011; Kokkoris et al, 2012; Aydogdu et al, 2013 and Pickering & Endre, 2013). They were published in English language between 2010 and 2013. These eligible articles were summarized in the PICO format table (appendix 5). The selected studies were either prospective observational or cohort studies that evaluated the investigative performance of plasma NGAL in detecting AKI and they used creatinine (serum or plasma) to identify AKI by elevation in serum or plasma creatinine $\geq$ 50% or $\geq$ 0.3 mg/dL from the baseline. Five studies were conducted in a single center, whereas one study (Pickering & Endre, 2013) was carried on in two centers, thus its findings were generalized and its validity was high. A total of 1,516 participants was included in these studies. These studies have been done in 6 countries.

Looking at the quality of the studies, neither partial nor differential verification biases were included because, in all the studies the participants received the same reference standard. All the studies used creatinine in blood (plasma or serum) as a gold standard, which is the appropriate reference standard for identifying AKI. Moreover, all studies described text execution of the diagnostic test, thus the findings of these studies are reliable since they allow test repetition. Cruz et al (2010) and Aydogdu et al (2013) studies did not have statistical information about serum creatinine, thus it may show a report bias. However, only three studies Constsntine et al (2010), Cruz et al (2010) and De Geus et al (2011) were conducted blindly as double and single blind respectively; therefore the review bias was avoided.

The intervention (pNGAL) was measured at ICU entry, then after ICU entry at 4, 8, 24, 36, 48, 60, 72 hours. It measured by a Triage meter in all of the studies except Aydogdu et al (2013) study that measured it by enzyme linked immunosorbent assay (ELISA). Creatinine in blood examined at ICU admission and then daily in all of the studies. The baseline value of creatinine was used the lowest value from previous patient's records; if it was not available the ICU admission value was used.

The outcome measure of the selected articles was measured by the area under the curve (AUC) in all studies except the study of Constantin et al (2010) was used mean ± SD to measure serum creatinine. These statistical measures were correlated with *P* value to identify the significant differences (*P <0.05* is considered significant). The studies of (Constantin et al (2010); Cruz et al (2010); De Geus et al (2011); Kokkoris et al (2102) and Pickering & Endre (2013)) reported that pNGAL was able to detect AKI in critically ill patients without AKI at ICU admission, while the study by Aydogdu et al (2013) reported that pNGAL was not specific to detect AKI with AUC = 0.44. Table 4 shows the finding of all the studies.

Table 4: AUC, mean ± SD and *P* value presents the performance of pNGAL and plasma or serum creatinine (SCr).

Study	AUC or mean ± SD	*P* value
Constantin et al (2010)	pNGAL: 0.956 (95% CI, 0.864 - 0.992) sCr: 185 ± 58[a]	*P* = 0.0001
Cruz et al (2010)	pNGAL: 0.078 (95% CI, 0.65 – 0.90) sCr: NA	NA
De Geus et al (2011)	pNGAL: 0.75 ± 0.10[b.] sCr: 0.65 ± 0.10[b]	*P* < 0.001
Kokkoris et al (2012)	pNGAL: 0.777 (95% CI, 54.8 – 85.8) sCr: 0.765 (95% CI, 54.8 – 85.8)	*P* = 0.001
Aydogdu et al (2013)	pNGAL: 0.44 sCr: NA	NA
Pickerning & Endre (2013)	pNGAL: 0.92 (95% CI, 0.76 – 1.0) pCr: 0.70 (95% CI, 0.48 – 0.92)	*P* = 0.06

a: mean ± SD, b: AUC, NA: Not Applicable.

DISCUSSION

The objective of this review is to find out the best literatures that investigate the diagnostic performance of pNGAL in detecting AKI in critical ill patients without AKI at ICU admission compared with creatinine in the blood. All studies showed that pNGAL is a good marker to detect AKI except the study by Aydogdu et al (2013) reported that it was not specific with AUC of 0.44 and *P* = 0.44. The studies (Constantin et al, 2010); (De Geus et al, 2011); (Pickering & Endre 2013)) showed significant differences between pNGAL and creatinine with *P* = 0.0001, *P* < 0.001 and *P* = 0.06 respectively. While Kokkoris et al (2012) stated no statistical significance difference between the two test (*P* = 0.0001).

The participant's sample size is measured as one of the major significant criteria to appraise the power of the study (Aveyard & Sharp, 2009). A power calculation by survey software was conducted to estimate the required participant's number in all studies (CRS, 2012). All studies used large sample size. Two studies used 99% from the total participants (Constantin et al, 2010; Kokkoris et al 2012), Cruz et al (2010) used 98%, De Geus et al (2012) used 96%, Pickering & Endre (2013) used 97.5% and Aydogdu et al (2013) used 100%. This supports the finding since the large sample size leads to more precision (Jones et al, 2003).

The age was restricted to adult > 19 years. However, the included age in these studies was between young adult (<65 years) and elderly (> 65 years). The elderly patients have a higher prevalence of AKI because of their attributed to different comorbid states that could cause AKI (Coca, 2012). This illustrates the verities in pNGAL performance among the studies.

The first time of pNGAL measurement was different among the studies. It was obtained within 1 hour of enrollment in Cruz et al (2010) and Kokkoris et al (2012), within 2 hours in Constantin et al (2010), on admission in De Geus et al (2011), but in case it missed the sample replaced by the 4 or 8 hours samples, Aydogdu et al (2013) within 24 hour enrollment and Pickering & Endre (2013) measured it at admission. This may influence the finding as the time of renal injury is unknown in ICU population, so the patient may develop AKI before the first measurement and this causes the variation in the predictive values of pNGAL among the studies. In addition, pNGAL elevated within 1 – 3 hours after cardiac surgery and 2 - 6 hours in other conditions (Maisel et al, 2011) which explore the relationship between pNGAL measurement timing and the AKI diagnosis.

Moreover, all studies measured pNGAL by Triage meter except the study by Aydogdu et al (2013) which measured it by enzyme linked immunosorbent assay (ELISA). Both methods have a high correlation (r = 0.94) and both can measure the 2 hours of pNGAL elevation value, hence pNGAL at this measurement time is considered an excellent test to predict AKI development (Dent et al, 2007). Consequently, the measurement's method does not affect the finding since both assays give the same results.

However, all studies measures creatinine in serum specimen except Pickering & Ender (2103) study that measured creatinine in plasma specimen. Beside that all studies used RIFLE/AKIN criteria to define AKI. Moreover the serum or plasma creatinine baseline value was obtained from previous medical records of the

patients in all the studies and when it was not available the ICU admission value for serum or plasma creatinine was taken as a baseline. This could influence the finding as the disease is observed from the baseline, and whenever the baseline was taken from previous records, the time of renal insult may missed. As the baseline was taken from the lowest value which ranged from1 month to 1 or2 years among the studies; so in this period any change in creatinine might occur due to the severity of the illness. Although, the baseline of creatinine from the lowest value of the previous ≥ 3 months is recommended currently (Candela-Toha et al, 2012). Despite that, this could be a source of reporting bias in terms of the early diagnosis by overestimation or underestimation. On the other hand, using of ICU admission value of creatinine could reduce the diagnosis, since at ICU admission some patients may have AKI, and their NGAL could be higher that interfering with its performance to detect the AKI prognosis (Chen et al, 2012), from this point, the non-specific performance of pNGAL stated by Aydogdu et al (2013) could be due to those factors.

However, the studies by constantin et al (2010), De Geus et al (2011), Kokkoris et al (2012) and Pickering & Endre (2013) had statistical information about the level of pNGAL, creatinine in blood and the significant differences between them and this avoid reporting bias, while Cruz et al (2010) and Aydogdu et al (2013) had no statistical information about creatinine in blood and this could present reporting bias and decrease the validity of the results in terms of focusing on the intervention more than the comparison. Despite the significant of the intervention, the significant differences between it and the comparison will make the results more valid and reliable.

Limitation of the review

All articles were available in limited internet access. In addition, one study was scanned by the title and it was relevant to the PICO question, but the full text was in French language and it excluded as non- English studies were excluded, and this leads to neglecting any strong literature published in non-English (Cluett, 2006). Conversely, the review includes a good quality studies with large sample size.

RECOMMENDATION

Plasma NGAL is recommended to be implemented in the clinical practice due to its significant performance and its possible measurement with the current available machines like ELISA. Despite that, large multicentre comparative studies are recommended to generalize the findings with measuring pNGAL at ICU entry in order to prevent over or underestimation of AKI diagnosis.

CONCLUSION

Key messages raised from this review are: pNGAL performance affected by its measurement time. AKI is prevalent in elderly patients than the other adult patients. This review concludes that pNGAL is able to detect AKI as it will add an early diagnosis and management of AKI among critical illnesses.

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