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Research Article

Relationship of Body Mass Index and Clinical Outcomes in Patients with Acute Kidney Injury: Systematic Review and Meta-analysis

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Abstract

Background: A higher body mass index (BMI) is considered as risk factor of developing chronic kidney diseases. However, its impact on acute kidney injury (AKI) remains debatable. This meta-analysis aimed to scrutinize the research evidence regarding the association of BMI and AKI development.

Methods: Eligible studies published until August, 2021 were searched by using electronic databases. Review Manager (RevMan) was used to evaluate the association of BMI and AKI by considering the odd ratio (OR) with 95% confidence interval (CI). Sensitivity analysis and publication bias were assessed.

Results: A total of 69,190 participants were obtained from 15 included studies. The pooled results show that the overall AKI incidence was 24.9%. OR of AKI in obese, overweight, and underweight were 1.22, 95% CI: 0.98 to 1.52, 1.2, 95% CI: 1.01 to 1.42, and 0.9, 95% CI: 0.78 to 1.02 respectively. AKI mortality was associated with underweight group with OR of 1.45, 95% CI: 1.04 to 2.01. AKI stages were statistically insignificant.

Conclusion: High incidence of AKI and high AKI mortality rate are associated with elevated BMI and low BMI respectively, hence awareness and control measures on BMI should be taken into account to prevent AKI burden. Further studies are recommended.

Keywords: AKI; BMI; Clinical outcome

Abbreviations

AKI: Acute Kidney Disease; APACHE: Acute Physiology and Chronic Health Evaluation; BMI: Body Mass Index; BUN: Blood Urea Nitrogen; CI: Confidence Interval; eGFR: estimated Glomerular Filtration Rate; LOS: Length of Stay; ICU: Intensive Care Unit; OR: Odd Ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO: International Prospective Register of Systematic; SD: Standard deviation

Background

Despite BMI's consideration as a tool for evaluating the nutritional status, its increment remains associated with different health comorbidities such as cardiovascular diseases, type 2 diabetes, and chronic kidney diseases [1-5].

The impact of overweight and obesity as a global epidemic is intense. BMI average is raising over 0.4 to 0.5 kg/ m2 in each decade worldwide [6]. It has been stated that 39% of adults were overweight in 2016. In 2020, 39 million of under 5 years old were overweight or obese, and the trend estimates that 2.7 billion adults will be overweight in 2050 globally [7-9]. In USA, the severe obesity folded over 9.2% from 2000 to 2018 [10]. In similar vein, a study carried out in England reports that overweight rate is increasing up to 40% in men [11]. Based on the aforementioned studies, a growing rate of BMI in global and regional is alarming. A rationale for researchers to explore the association of BMI and other diseases.

In the past decades, obesity-related nephropathy has been recognized due to several factors including type 2 diabetes, hypertension, intraglomerular pressure, and glomerulomegaly resulting in chronic kidney diseases [12]. Currently, findings show that AKI-obesity is associated a high number of patients in intensive care unit (ICU) [13]. 25% of ICU patients are obese with OR of 1.89 compared to general population [14]. So far, the confounding results have been found. Some studies established that more BMI is correlated with high prevalence of AKI and ICU- mortality compared to normal BMI, whereas, others proved that high mortality rate exists in underweight compared to overweight [15,16]. Therefore, the current meta-analysis aimed to scrutinize the research evidence regarding the association of BMI and AKI as the outcome of critically ill patients which remains inconsistent.

Methodology

Protocol and registration

This meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. The protocol was registered in International Prospective Register of Systematic (PROSPERO) database (Registration number: CRD42021272156).

Searching strategies

An electronic search was conducted in Pubmed, Embase, Medline, Google Scholar, and Scopus databases for retrieving the

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Table 1: Details of the included studies.

Author, Year, Reference	Study design	Country	Population n	Number with BMI/total patients (%)	Aim of the study	Comorbidities	Outcomes
Vasquez 2020 [19]	Prospective cohort study	USA	463	463/553 (84%)	BMI and AKI after severe trauma	Hypertension, Diabetes mellitus, chronic kidney disease, and congestive heart failure	-
Zou 2017 [20]	Retrospective study	China	8,455	8,455/13083 (65%)	BMI and AKI after cardiac surgery	Hypertension and Diabetes mellitus,	AKI mortality, duration of mechanical ventilation, LOS in ICU, and LOS in hospital
Ju 2018 [21]	Retrospective study	Korea	468	468	BMI as AKI predictor in critically ill patients	diabetes mellitus, hypertension; cardiovascular disease; liver cirrhosis; chronic kidney disease; and acute respiratory distress syndrome	APACHE II score, SOFA score, ICU admission, MV duration, ICU LOS, hospital LOS, ICU death, and hospital death
Argalious 2017 [22]	Retrospective	USA	8,543	8,543/121,745 (7%)	BMI and AKI after laparoscopic surgery	Diabetes mellitus, hypertension; coronary artery disease, and chronic obstructive pulmonary disease	AKI and hospital mortality
Park 2017 [23]	Retrospective study	Korea	203	203/334 (61%)	BMI and AKI in liver transplantation recipients	hepatitis B virus; hepatitis C virus, Primary biliary cirrhosis, Autoimmune hepatitis, hypertension, and diabetes mellitus	AKI incidence, ICU stay, hospital stay, and hospital mortality
Kim 2018 [24]	Observational study	Korea	1,144	1144/2391 (48%)	BMI and AKI in renal replacement therapy	Cancer, diabetes mellitus, hypertension, myocardiac infarction, congestive heart failure, cerebrovascular attack, peripheral vascular disease, and chronic obstructive pulmonary disease	AKI , APACHE II, and SOFA
Wang 2019 [25]	Retrospective cohort study	China	1120	1120/1271 (88.1%)	BMI and AKI in renal replacement therapy	Myocardial infarction, congestive heart failure, cerebrovascular disease, diabetes mellitus, and hypertension	-
Kim 2017 [26]	Observational study	Korea	212	212/573 (36.9)	BMI and AKI in renal replacement therapy	Diabetes mellitus, hypertension, congestive heart failure, cerebrovascular attack, and cancer	Mortality, hospital LOS, and ICU LOS
Liu 2021 [27]	Retrospective cohort study	China	115	115/137 (83.9)	BMI and AKI after aortic arch surgery	Cerebrovascular disease, diabetes mellitus, hypertension, and kidney malperfusion	postoperative AKI, Length of ICU, length of in hospital, and hospital mortality
Liu 2018 [28]	Retrospective cohort study		12,555	12555/35474 (35.3%)	BMI and AKI	Hypertension, hypertension, and cardiovascular disease	AKI, mortality within 90 days of admission, and length of stay
MacLaughlin 2021 [29]	Prospective multisite cohort study	USA	1477	1477/1603 (92.1%)	BMI and Chronic kidney disease after AKI	Diabetes, chronic heart failure, and cardiovascular disease	AKI stages, ICU, and hospital mortality
Gameiro 2018 [30]	Retrospective cohort study	Portugal	456	456/722 (63.1%)	Obesity and AKI in patients with sepsis	Hypertension, diabetes, and infection	AKI, LOS in hospital, LOS in ICU, ICU mortality, and hospital mortality
Sabaz 2021 [13]	Retrospective cohort study	Turkey	4,459	4459/7227 (61.6%)	BMI on AKI and ICU mortality	Hypertension, Diabetes, Cerebrovascular disease, Malignancy, Hepatic disease, Psychiatric disorder, Dementia, chronic obstructive pulmonary disease, chronic renal failure, coronary artery disease, and gastrointestinal bleeding	AKI, mechanic ventilation, APACHE 2, SOFA, and LOS in ICU
Zhou 2020 [31]	Retrospective cohort study	China	244	244/341 (71.5%)	Overweight and AKI after liver transplantation	Hypertension, diabetes mellitus, chronic kidney disease, encephalopathy, ascites, and liver disease	AKI and hospital mortality
Wang 2021 [32]	Retrospective cohort study	China	15174	-	BMI and AKI in critically ill patients	Congestive heart failure, cardiac arrhythmias, valvular disease, hypertension, renal disease, Liver disease, uncomplicated and complicated diabetes, metastatic cancer and coagulopathy,	AKI stage, SOFA, ICU LOS, and mortality
Moon 2018 [33]	Retrospective cohort study	Korea	3018	3018/3089 (97.7%)	Obesity and AKI after coronary artery bypass grafting	Hypertension, and diabetes mellitus,	AKI
Pedersen 2016 [35]	Regional cohort study	Denmark	13529	11411/16111 (70.8)	BMI and AKI after hip fracture surgery	Chronic kidney disease, diabetes, and Charlson comorbidity	AKI, mortality and hospital stay

articles published until August, 2021. The search term with Boalean Operators used were: "BMI" OR "body mass index" OR "overweight" OR "obese" OR "normal weight" OR "underweight" AND "acute kidney disease" OR "AKI" OR "kidney injury" OR "kidney failure". The language applied was English.

Inclusion and exclusion criteria

The study included the original articles that evaluated the association of BMI and AKI. The first criterion was if the participants were classified into underweight, normal weight, overweight, and obese. The second criterion was the analyzed outcomes which were included but not limited to, AKI development, AKI stage, intensive care unit stay, time used to stay in hospital, comorbidities (hypertension and diabetes mellitus). The excluded studies in meta-analysis were reviews, case reports, newspapers, conference papers, comments, and other studies that were not published in English and those conducted on the participants who are under 18 age old.

Study selection

Based on eligibility criteria, two independent reviewers screened the selected studies. They firstly removed the duplicates and other studies based on exclusion criteria by screening the titles and abstracts. The full-text of remaining studies were further revised for checking their eligibilities. Any discrepancies between the two investigators were solved by a third reviewer in mutual consensus.

Data extraction and quality assessment

The data were extracted by two independent authors based on a standardized form which is recommended by Cochrane. The extracted information was year of publication, design of study, country, participants' demographic features (age, height, weight, and gender), and outcomes: glomerulus filtration rate features, AKI mortality, AKI stage, LOS in ICU, LOS in hospital, acute physiology and chronic health evaluation (APACHE II). Participants group was classified as underweight, normal, overweight, and obese based on BMI $<18.5 kg/m^2$, BMI $\geq 18.5 < 25 kg/m^2$, BMI $\geq 25 < 30 kg/m^2$, BMI $\geq 30 kg/m^2$ respectively. Newcastle-Ottawa quality assessment tool was used to assess the quality of the cohorts and the risk of bias [18], more than six stars were considered as high quality to meet the eligibility criteria in meta-analysis. A funnel plot was used to evaluate the publication bias (more or equal to six included studies were considered).

Statistical analysis

Statistical analysis was executed by RevMan 5.0.25 (Nordic Cochrane Centre, Cochrane Collaboration, UK). Mann-Whitney U test was used to evaluate the hypothesis and $P < 0.05$ was considered as statistical significance. For continuous and dichotomous data, mean difference and OR in 95% CI were calculated respectively. A random effect model was used to assess the pooled OR and 95% CI. I^2 was used to assess the heterogeneity, where 0% to 40%, 30% to 60%, 50% to 90%, and 90% to 100% was considered as minimal, moderate, substantial, considerable heterogeneity respectively, and $P < 0.1$ designated the significance. Sensitivity analysis was used to assess the consistence of results.

Results

Study flow and characteristics

A total of 284,212 articles were retrieved through online searching the different databases including PubMed (169,107), Embase (57,726),

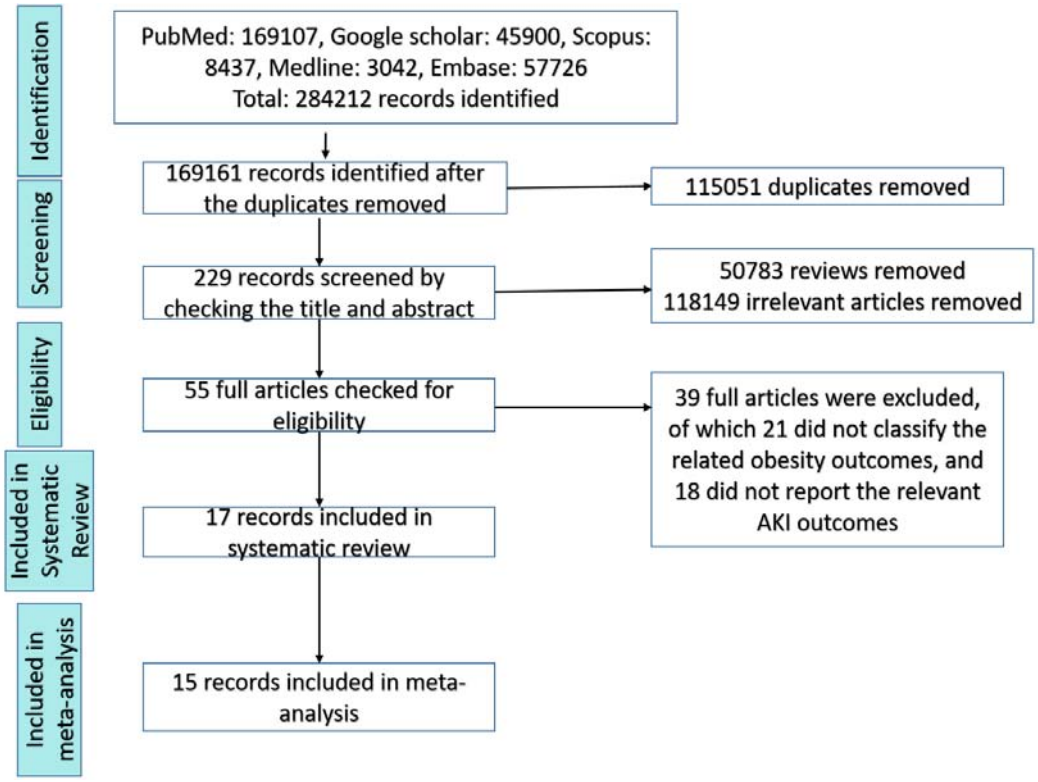

Figure 1: Workflow Chart.

Table 2: Details on patients' baseline features.

Author year, Ref	BMI (kg/m²) categories	Age, years, median (SD)	Hypertension (%)	Albumin baseline, g/L	UA baseline, μmol/L	eGFR baseline, mL/min	SCr baseline, μmol/L	BUN baseline, mmol/L	Height, cm	Body weight, kg	Male, *n* (%)	Diabetes mellitus, *n* (%)
Pedersen 2016 [35]	Underweight	84 (78-89)	-	-	-	-	-	-	-	-	168 (13.2%)	70 (5.5%)
	Normal	84 (78-89)	-	-	-	-	-	-	-	-	1817 (27.6%)	651 (9.9%)
	Overweight	82 (76-87)	-	-	-	-	-	-	-	-	938 (33.9%)	480 (17.3%)
	Obese	80 (74-86)	-	-	-	-	-	-	-	-	201 (25.7%)	206 (26.3%)
Zou 2017 [20]	Normal	52.6 ± 14.1	1,042 (23.6)	40.2 ± 3.6	354.7 ± 117.4	91.9 ± 25.1	77.4 ± 25.3	6.6 ± 2.9	163.4 ± 7.2	58.0 ± 6.6	2,251 (51.0)	292 (6.6)
	Overweight	55.3 ± 12.2	59.4 (16.7)	40.3 ± 3.3	377.8 ± 141.8	89.3 ± 23.1	80.9 ± 24.0	6.3 ± 2.2	166.4 ± 7.0	71.2 ± 6.8	1,644 (65.1)	307 (12.2)
	Obese	55.0 ± 11.9	344 (48.9)	40.4 ± 3.1	396.0 ± 109.5	87.3 ± 23.1	83.0 ± 24.4	6.3 ± 2.0	166.1 ± 8.0	83.0 ± 8.2	471 (66.9)	111 (15.8)
	Underweight	47.8 ± 16.6	97 (12.0)	39.8 ± 4.1	342.0 ± 114.6	98.2 ± 28.6	73.4 ± 25.0	6.6 ± 3.0	163.6 ± 7.3	46.0 ± 5.2	340 (42.2)	38 (4.7)
Ju 2018 [21]	Normal	68.6 ± 14.1	-	-	-	-	-	-	-	-	197 (41)	94 (33.0)
	Overweight	64.9 ± 13.8	44 (55.0)	-	-	-	-	-	-	-	47 (7)	34 (42.5)
	Obese	57.0 ± 15.9	-	-	-	-	-	-	-	-	116 (63.4%)	-
	Underweight	71.3 ± 12.7	34 (33.3)	-	-	-	-	-	-	-	62 (13)	27 (26.5)
Argalious 2017 [22]	Normal	54 ± 17	461 (31)	-	-	-	-	-	-	-	391 (26)	107 (7)
	Overweight	57 ± 15	7354 (44)	-	-	-	-	-	-	-	644 (39)	243 (15)
	Obese	56 ± 14	700 (56)	-	-	-	-	-	-	-	394 (31)	253 (20)
	Morbidly obese	49.3 ± 13.1	-	-	-	-	-	-	-	-	23 (31.1%)	26 (35.1%)
	Underweight	49 ± 17	21 (21)	-	-	-	-	-	-	-	20 (20)	2 (2)
Park 2017 [23]	Normal	54.38 ± 7.33	14 (18.9)	-	-	-	-	-	-	-	58 (78.4)	21 (28.4)
	Underweight	53.68 ± 8.91	9 (24.3)	-	-	-	-	-	-	-	26 (70.3)	14 (17.0%)
Kim 2018 [24]	Normal	65.0±13.6	217 (53.8)	2.6±0.6	35 (8.7)	33.1±22.3	2.5±1.3	35 (8.7)	-	-	241 (59.8)	140 (34.7)
	Overweight	63.9±14.0	110 (50.0)	2.6±0.6	21 (9.5)	32.7±24.4	2.9±1.9	21 (9.5)	-	-	155 (70.4)	79 (35.9)
	Obese	61.3±14.5	233 (55.3)	2.6±0.6	46 (10.9)	29.0±18.8	2.9±1.7	46 (10.9)	-	-	248 (58.7)	153 (36.3)
	Underweight	62.3±17.2	40 (40.4)	2.5±0.5	13 (13.1)	33.2±18.0	2.6±1.5	13 (13.1)	-	-	61 (61.6)	27 (27.6)
Wang 2019 [25]	Normal	64.85±13.73	216 (53.87)	-	-	-	32.44±22.51	55.83±28.07	-	-	242 (60.3)	138 (34.41)
	Overweight	63.94±13.61	113 (50.45)	-	-	-	31.75±22.63	56.79±31.36	-	-	154 (68.7)	83 (37.05)
	Obese	61.24±14.59	224 (55.31)	-	-	-	28.86±18.52	54.57±29.82	-	-	238 (58.7)	146 (36.05)
	Underweight	63.10±17.48	38 (42.22)	-	-	-	35.22±22.51	60.70±35.26	-	-	53 (58.8)	22 (24.72)
Liu 2018 [27]	Normal	63 ± 19.5	1579 (36.4)	-	-	-	-	-	-	-	2329 (53.7)	1039 (23.9)
	Overweight	62 ± 17.3	1519 (38.9)	-	-	-	-	-	-	-	2264 (58.0)	1072 (27.5)
	Obese	57 ± 15.9	1144 (44.2)	-	-	-	-	-	-	-	1306 (50.5)	837 (32.4)
MacLaughlin 2021 [29]	Underweight	70 ± 19.4	653 (37.8)	-	-	-	-	-	-	-	856 (49.6)	341 (19.7)
	Normal	64.3 (16.0)	-	-	-	-	70 (31)	-	-	-	88 (65.6)	43 (32)
	Overweight	65.9 (12.7)	-	-	-	-	64 (25)	-	-	-	174 (78)	87 (39)
	Obese	62.3 (11.2)	-	-	-	-	65 (26)	-	-	-	248 (62.6)	253 (64)
	Underweight	61.7 (15.1)	-	-	-	-	74 (36)	-	-	-	9 (56.2)	4 (25)
Gameiro 2018 [30]	Normal	63.9±16.5	141 (43)	1.9±0.6	-	-	-	-	-	-	203 (61.3)	63 (19)
	Obese	64.4±14.8	71 (56.8)	1.9±0.5		-	-	-	-	-	61 (48.8)	40 (32)
Sabaz 2021 [13]	Normal	57.88±21.53	495 (27.5)	-	-	-	-	-	-	-	1153 (64)	270 (15.0)
	Overweight	61.16±18.0	662 (37.4)	-	-	-	-	-	-	-	1088 (61.5)	397 (22.4)
	Obese	64.69±15.53	481 (54.2)	-	-	-	-	-	-	-	258 (29.1)	326 (36.7)
Zhou 2020 [31]	All participants	54.8 (9.6)	69 (28.04)	-	-	-	-	-	-	-	244 (99)	86 (34.9)
Wang 2021 [32]	Normal	81.42 ± 61.16	749 (15.99)	-	-	-	-	26.39 ± 21.27	-	-	2683 (57.29)	1087 (23.2)
	Overweight	74.72 ± 47.22	815 (16.03)	-	-	-	-	26.03 ± 20.38	-	-	3412 (67.11)	1481 (29.1)
	Obese	66.80 ± 31.95	824 (16.38)	-	-	-	-	28.21 ± 21.77	-	-	2973 (59.12)	2125 (42.2)
	Underweight	87.05 ± 71.09	55 (14.55)	-	-	-	-	26.59 ± 21.97	-	-	153 (40.48)	65 (17.1)

Moon 2018 [33]	Normal	66.7 ± 9.88	53.4	3.7 ± 0.46		69.7 ± 20.74	-		-	-	836 (74.0)	43.2
	Overweight	64.7 ± 9.48	60.4	3.8 ± 0.65		70.2 ± 19.63	-	-	-	-	493 (77.4)	45
	Obese	60.0 ± 11.60	72.7	3.9 ± 0.60		73.4 ± 20.06	-	-	-	-	829 (70.2)	49.6
	Underweight	70.8 ± 9.95	53.5	3.7 ± 0.60		66.0 ± 23.59	-	-	-	-	44 (62)	28.2
Vasquez 2020 [19]	All participants	42 (28-60)	127 (27.4)	-	-	-	-	-	-	-	350 (75.5)	31 (6.6)
Liu 2021 [27]	All participants	48.7±10.4	92 (80)	-	-	-	-	-	-	-	86 (74.7)	7 (6.08)
Kim 2017 [26]	All participants	61.8 ± 13.2	100 (47.1)	-	-	-	-	-	-	-	138 (65.09)	58 (27.3)

Medline (3,042), Google Scholar (45,900), and Scopus (8,437). A total of 115,051 duplicates were removed, resulting in 169,161 articles which screened for the title and abstract. Subsequently, 229 articles were identified after removing 50,783 narrative reviews and 118,149 irrelevant articles. Among 55 full articles which checked for eligibility, 39 articles were excluded due to the lack of the related report of BMI and AKI outcomes. 17 articles were included in systematic review and 15 articles were considered in meta-analysis (Figure 1).

A total of 69,190 participants were included in these studies which carried out in 7 countries namely China (n=4), Denmark (n=1) Korea (n=4), Portugal (n=1), Turkey (n=1), Singapore (n=1), and USA (n=3). Study design in all studies was retrospective, except one which was a prospective study (Table 1).

The male participants who included in the studies were 33,478/69,190 (48.3%), and the range of mean age was 47.8-87.05. More about patients' baseline features including albumin, uric acid, estimated glomerular filtration rate (eGFR), serum creatinine, and blood urea nitrogen (BUN) baseline, height, weight, and comorbidities like hypertension, and diabetes mellitus were summarized in Table 2.

Quality assessment

The Newcastle-Ottawa tool was used to determine the quality of each eligible study. The maximum star designed for each study was nine: four stars for selection, two stars for comparability, three stars for the outcome. A study with greater or equal to seven stars was considered as high quality. Among seventeen studies, seven studies [13,23,28-30,32,35] scored eight points, eight studies [19,21,22,24-26,29,31] scored seven points and two studies [27,33] scored six points (Supplementary Table 1). Meta-analysis included fourteen study based on the quality scale. There was no obvious risk of publication bias which was assessed based on funnel plot (Supplementary 1 Figure 1).

Overall analysis

Based on BMI, the current systematic review assessed the different patient's outcomes in the included studies including AKI incidence, AKI mortality, length of stay in intensive care (LOS in ICU), and APACHE II score. Among these studies, the highest incidence of AKI, AKI mortality, ICU mortality, Hospital mortality, highest APACHE II score, long stay in ICU, and long stay in hospital were found in obese population (92.8 %), underweight population (9.5%), overweight population (43.8%), underweight population (70.7%), overweight population (27.5 ± 9.1), underweight population (44 (20, 95)), underweight population (35 (14–222)) respectively, as they are summarized in Table 3. Table 4 summarizes the percentage of comorbidities (hypertension and diabetes mellitus) in different groups. The overall percentage of hypertension and diabetes mellitus was 34.4% and 20.03% respectively. The highest percentage of hypertension (46.2%) and diabetes (34.3%) was in obese group. The percentage of hypertension in underweight, normal-weight, and overweight was 19.9%, 26.9%, and 31.4% respectively. The percentage of diabetes mellitus in underweight, normal-weight, and overweight was 5.9%, 13.4%, and 19.9% respectively.

BMI and AKI

The incidence of AKI among the included studies in meta-analysis was 24.9%. The subgroups analysis shows that the highest incidence was 30.1% in overweight population, and the smallest was 18% in underweight group (Table 5).

The risk of developing AKI in the overweight group was more likely than normal-weight group, OR was 1.2, 95% CI: 1.01 to 1.42, P=0.03), there was substantial heterogeneity among overweight studies with I^2=78%, P=0.0001. The association of AKI in obese group was more likely higher than in normal group, even it is not statistically significant, OR was 1.22, 95% CI: 0.98 to 1.52, P=0.08, there was substantial heterogeneity with I^2=86%, P=0.00001. The results in underweight group show that 10% were less likely to develop AKI compared to normal-weight group, even it was not statistically significant, OR was 0.9, 95% CI: 0.78 to 1.02, P=0.11, with a minimal heterogeneity, I^2=7%, P=0.38 as shown in Figure 2a-2c. A sensitivity analysis were conducted after removing the outlier in underweight and overweight group, results remain consistent to the primary findings. However, in the overweight group, the sensitivity analysis shows the statistical significant results with OR of 1.32, 95% CI: 1.16 to 1.5, I^2=36%, P=0.0001 (Supplementary 2 Figure 1).

BMI and AKI stage 1: The overall analysis of BMI and AKI stage 1 in six and seven included studies shows that 4% underweight and 5% obese patients were less likely to experience AKI stage 1 compared with normal population, with OR of 0.96, 95% CI: 0.74 to 1.6, P=0.77 and 0.95, 95% CI: 0.74 to 1.22, P=0.69, but, both findings were not statistically significant. The results reveal that overweight patients were slightly more likely to experience AKI stage 1 compared to normal-weight, even if it was not statically significant, OD was 1.01, 95% CI: 0.91 to 1.11, p=0.90. There was a moderate heterogeneity in underweight group with I^2=53%, P=0.06, a minimal heterogeneity in overweight group with I^2=26%, P=0.23, and a substantial heterogeneity in obese group with I^2=81%, P=0.0001 (Figure 3a-3c).

BMI and AKI stage 2: The overall meta-analysis of BMI and AKI stage 2 demonstrates that 8% in underweight (seven studies) and overweight (eight studies) sub-groups are less likely to develop AKI stage 2, but not statistically significant, the OR in underweight and overweight group were 0.92, 95% CI: 0.57 to 1.46, P=0.71 and 0.92, 95% CI: 0.47 to 1.77, P=0.79, respectively. Conversely, obese

Table 3: Incidence of AKI and outcomes.

Author year	BMI (kg/m²) categories	AKI-RRT Incidence (%)	AKI mortality (%)	MV-free days	ICU mortality (%)	LOS in ICU	hospital length of stay	Hospital mortality	AKI-RRT mortality	AKI (%)	AKI STAGE 1 (%)	AKI STAGE 2 (%)	AKI STAGE 3 (%)	AKI stage 2-3 (%)	Renal replacement therapy	APACHE II score
Pedersen, 2016	Underweight (n=1272)	-	-	-	-	-	9 (5-13)	24 (23.1%)	-	128 (10)	96 (7.5%)	22 (1.7%)	10 (0.8%)	-	-	-
	Normal (n=6588)	-	-	-	-	-	10 (5-14) 6.6	97 (14.1%)	-	782 (11.9)	572 (8.7%)	158 (2.4%)	52 (0.8%)	-	-	-
	Overweight (n=2769)	-	-	-	-	-	10 (6-14)	35 (10.7%)	-	345 (12.4)	249 (9.0%)	69 (2.5%)	27 (1.0%)	-	-	-
	Obese (n=782)	-	-	-	-	-	11 (7-16)	20 (15.2%)	-	140 (17.9)	92 (11.8%)	33 (4.2%)	15 (1.9%)	-	-	-
Zou 2017	Normal	74/1,368 (5.4)	82/1,368 (6.0)	1 (1, 2)	-	40 (20, 88)	13 (10, 18)	-	45/74 (60.8)	1,368 (31.0)	1,010 (73.8)	205 (15.0)	153 (11.2)	358 (26.2)	-	-
	Overweight	44/922 (4.8)	35/922 (3.8)	1 (1, 2)	-	39 (20, 86)	14 (11, 18)	-	16/44 (36.4)	922 (36.5)	667 (72.3)	154 (16.7)	101 (11.0)	255 (27.7)	-	-
	Obese	17/324 (5.2)	14/324 (4.3)	1 (1, 2)	-	40 (19, 93)	14 (11, 18)	-	10/17 (58.8)	324 (46.0)	223 (68.8)	67 (20.7)	34 (10.5)	101 (31.2)	-	-
	Underweight	13/241 (5.4)	23/241 (9.5)	1 (1, 2)	-	44 (20, 95)	14 (10, 18)	-	9/13 (69.2)	241 (29.9)	161 (66.8)	51 (21.2)	29 (12.0)	80 (33.2)	-	-
Ju 2018	Normal	121 (42.3)	9.8 ± 19.8	10.3 ± 21.0	-	-	-	-	-	-	-	-	-	-	66 (23.1)	18.8 ± 8.8
	Overweight	-	-	7.4 ± 10.5	35 (43.8)	6.9 ± 9.8		40 (50.0)		29 (36.3)	-	-	-	-	28 (35)	21.4 ± 10.0
	Obese	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Underweight	-	-	10.7 ± 11.8	41 (40.2)	11.7 ± 13.4	-	48 (47.1)	-	10 (9.8)	-	-	-	-	19 (18.6)	16.7 ± 7.5
Argalious 2017	Normal	-	-	-	-	-	-	9 (0.6)	-	34 (2.3)	27 (1.8)	5 (0.3)	2 (0.1)	-	-	-
	Overweight	-	-	-	-	-	-	9 (0.5)	-	53 (3.2)	42 (2.5)	8 (0.5)	3 (0.2)	-	-	-
	Obese	-	-	-	-	-	-	5 (0.4)	-	37 (2.9)	28 (2.2)	5 (0.4)	4 (0.3)	-	-	-
	Morbidly obese	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Underweight	-	-	-	-	-	-	1 (1)	-	4 (4)	3 (3)	1 (1)	0	-	-	-
Park 2017	Normal	-	-	-	-	10.0 ± 8.8	26 (15-110)	2 (2.7)	-	30 (40.5)	23 (31.1)	7 (9.5)	0	-	-	-
	Underweight	-	-	-	-	12.41 ± 10.96	35 (14-222)	2 (5.4)	-	13 (35.1)	10 (27.0)	2 (5.4)	1 (2.7)	-	-	-
Kim 2018	Normal	-	-	-	-	9 (3-20)	20 (7-46)	256 (63.5)	-	-	-	-	-	-	-	27.4±8.0
	Overweight	-	-	-	-	6 (3-15)	23 (6.5-45.5)	136 (61.8)	-	-	-	-	-	-	-	27.5±9.1
	Obese	-	-	-	-	8 (3-16)	21 (8-41)	239 (56.8)	-	-	-	-	-	-	-	26.7±8.4
	Underweight	-	-	-	-	5 (2-14)	8 (2-30)	70 (70.7)	-	-	-	-	-	-	-	26.4±8.3
Wang 2019	Normal	-	-	319 (79.55%)	-	-	-	-	-	-	-	122 (30.42%)	279 (69.58%)	-	-	27.86±7.47
	Overweight	-	-	176 (78.57%)	-	-	-	-	-	-	-	67 (29.91%)	157 (70.09%)	-	-	27.64±8.57
	Obese	-	-	313 (77.28%)	-	-	-	-	-	-	-	90 (22.22%)	315 (77.78%)	-	-	26.77±8.13
	Underweight	-	-	70 (77.78%)	-	-	-	-	-	-	-	14 (15.56%)	76 (84.44%)	-	-	25.81±7.55
Liu 2018	Normal	-	-	-	414 (9.5)	5 (3-10)			-	564 (35.1)	-	-	-	-	-	-
	Overweight	-	-	-	239 (6.1)	4 (3-8)	-	-	-	488 (30.4)	-	-	-	-	-	-
	Obese	-	-	-	88 (3.4)	4 (2-7)	-	-	-	279 (17.4)	-	-	-	-	-	-
	Underweight	-	-	-	256 (14.8)	7 (4-14)	-	-	-	275 (17.1)	-	-	-	-	-	-
MacLaughlin 2021	Normal	-	-	-	-	-	-	-	-	-	100 (75%)	18 (13%)	16 (12%)	-	-	-
	Overweight	-	-	-	-	-	-	-	-	-	174 (78%)	25 (11%)	24 (11%)	-	-	-
	Obese	-	-	-	-	-	-	-	-	-	264 (67%)	75 (19%)	57 (14%)	-	-	-
	Underweight	-	-	-	-	-	-	-	-	-	15 (94%)	0	1 (6%)	-	-	-
Gameiro 2018	Normal	-	-	256 (77.3)	-	81 (24.5)	38.8±39.3	113 (34.1)	-	283 (85.5)	-	-	-	-	-	-
	Overweight	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Obese	-	-	94 (75.2)		27 (21.6)	32.6±39.3	40 (32)	-	116 (92.8)	-	-	-	-	-	-
	Underweight	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Sabaz 2021	Normal	-	-	4.81 (2.74-11.14)	548 (30.4)	5.45 (3-12.72)	-	-	-	1172 (65.1)	98 (5.4)	156 (8.7)	918 (51.0)	-	-	24 (17-29)
	Overweight	-	-	5.73 (2.51-12.16)	556 (31.4)	6.54 (2.84-13.58)	-	-	-	1149 (64.9)	118 (6.7)	185 (10.4)	846 (47.8)	-	-	25 (19-30)
	Obese	-	-	5.89 (2.75-12.47)	307 (34.6)	6.81 (3.32-13.88)	-	-	-	620 (69.8)	57 (6.4)	101 (11.4)	462 (52.0)	-	-	26 (19-31)
	Underweight	-	-	-	-	-	-	-	-		-	-	-	-	-	-

Zhou 2020	Normal	-	-	-	-	-	-	-	-	28.7	-	-	-	-	-	-
	Overweight	-	-	-	-	-	-	-	-	47.7	-	-	-	-	-	-
	Obese	-	-	-	-	-	-	-	-	50.50%	-	-	-	-	-	-
	Underweight	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Wang 2021	Normal	-	-	-	-	-	-	812 (17.34)	-	-	1079 (23.04)	786 (16.78)	2818 (60.18)	-	-	-
	Overweight	-	-	-	-	-	-	687 (13.51)	-	-	1119 (22.01)	749 (14.73)	3216 (63.26)	-	-	-
	Obese	-	-	-	-	-	-	667 (13.26)	-	-	920 (18.29)	811 (16.13)	3298 (65.58)	-	-	-
	Underweight	-	-	-	-	-	-	71 (18.78)	-	-	98 (25.93)	81 (21.43)	199 (52.65)	-	-	-
Moon 2018	Normal	-	-	-	-	-	-	-	-	25.6	-	-	-	-	-	-
	Overweight	-	-	-	-	-	-	-	-	26.7	-	-	-	-	-	-
	Obese	-	-	-	-	-	-	-	-	35.5	-	-	-	-	-	-
	Underweight	-	-	-	-	-	-	-	-	29.6	-	-	-	-	-	-

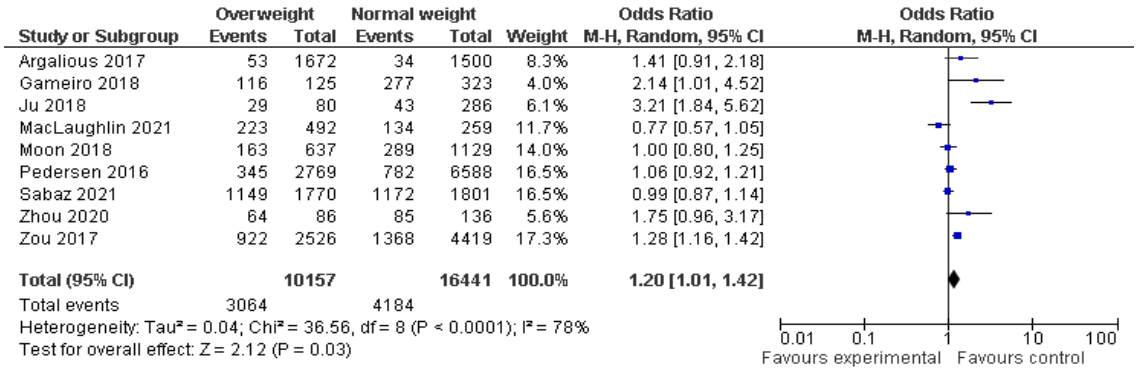

Figure 2a: AKI and Overweight.

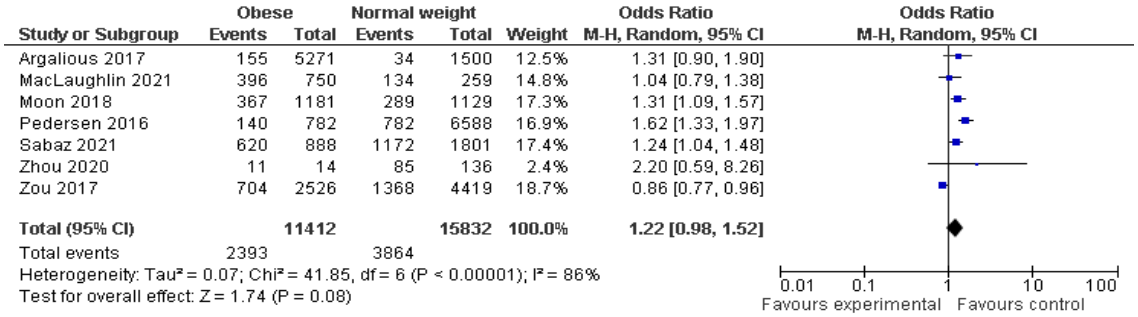

Figure 2b: AKI and Obese.

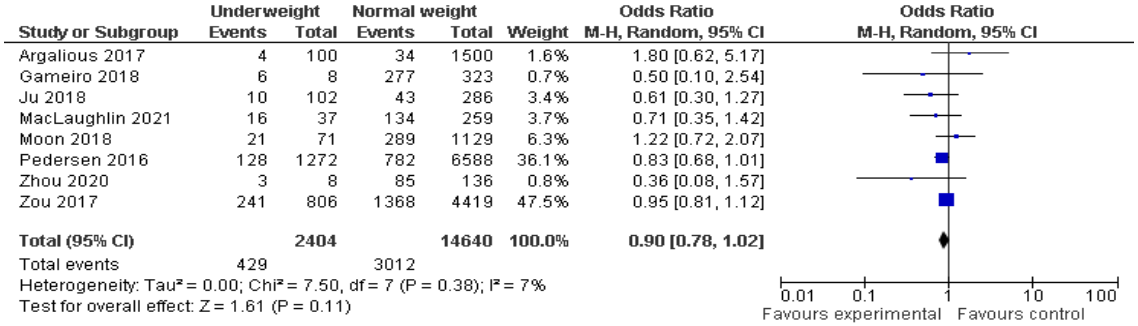

Figure 2c: AKI and Underweight.

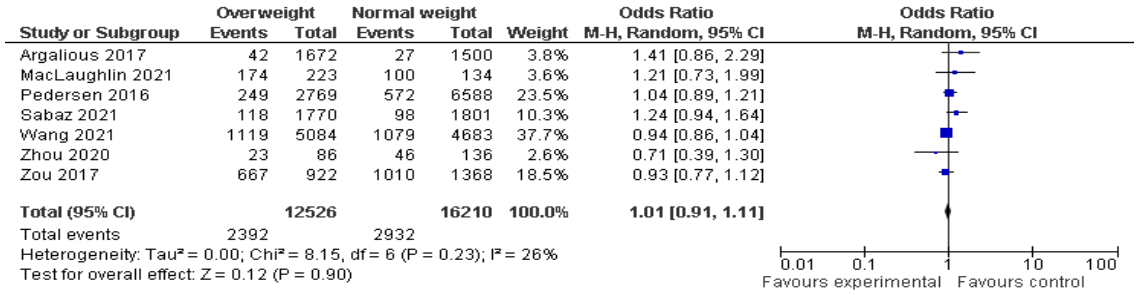

Figure 3a: AKI stage 1 and Overweight.

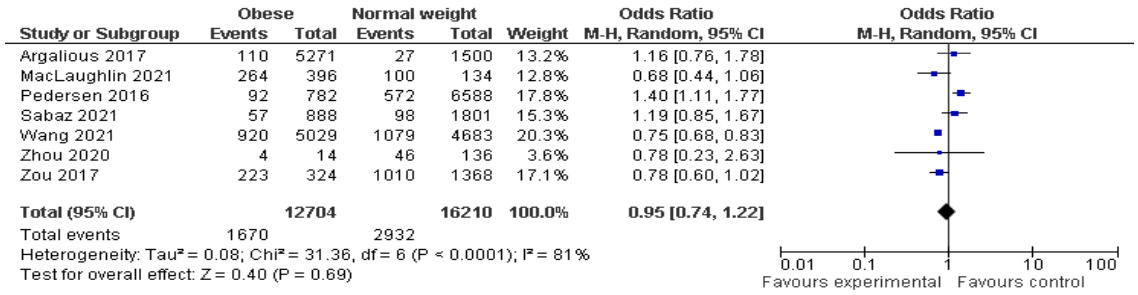

Figure 3b: AKI stage 1 and Obese.

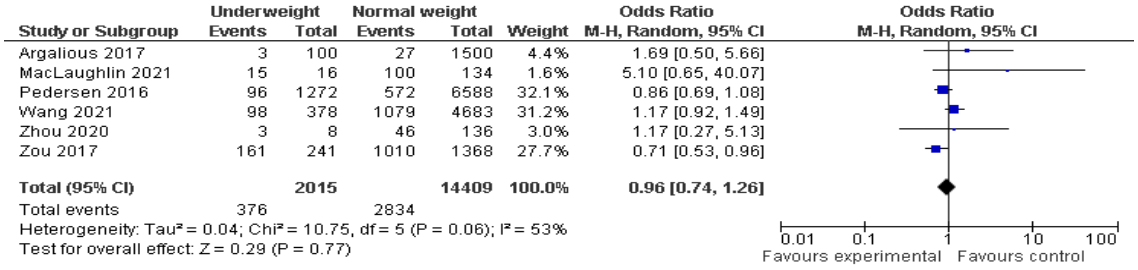

Figure 3c: AKI stage 1 and Underweight.

group (eight studies) was statistically insignificant more likely to develop AKI stage 2, OR was 1.24, 95% CI: 0.96 to 1.61, P=0.1. A substantial, considerable, and substantial heterogeneity with I^2=73%, P=0.001, I^2=98%, P=0.00001, and I^2=78%, P=0.0001 were found in underweight, overweight, and obese group respectively (Figure 4a-4c).

BMI and AKI stage 3: The pooled results of BMI and AKI stage 3 of seven studies show that obese population were more likely to develop AKI stage 3 with OR 1.27, 95% CI: 1.06 to 1.51, P=0.008. The other subgroups are also more likely to develop AKI stage 3, but not statistically significant, OR in underweight (seven included studies) and overweight (eight included studies) group were 1.08, 95% CI: 0.71 to 1.65, P=0.72 and 1.06, 95% CI: 0.90, 1.25, P=0.47, respectively. The studies are associated with moderate, moderate to substantial, and substantial heterogeneity with I^2=60%, P=0.02, I^2=60%, P=0.02, and I^2=62%, P=0.01 in obese, underweight, and overweight group respectively (Figure 5a-5c).

BMI and AKI stage 2-3: There was only one study which analyzed the association of BMI and AKI stage 2-3 development. The study showed that underweight population were more likely to develop AKI stage 2-3, OR was 1.4, 95% CI: 1.04 to 1.88, P=0.02. Moreover, the overweight and obese population were more likely to develop AKI stage 2-3, but not statistically significant, ORs were 1.08, 95% CI: 0.89 to 1.30, p=0.43 and 1.28, 95% CI: 0.98, 1.66, P=0.07 (Figure 6a-6c).

Table 4: Percentage of Comorbidities and BMI.

Comorbidities	Sub-group	Event	Total	Percentage
Hypertension	Underweight	335	1683	19.90%
	Normal-weight	4010	14885	26.90%
	Overweight	3996	12705	31.40%
	Obese	6771	14650	46.20%
	Total	15112	43923	34.40%
Diabetes mellitus	Underweight	154	2577	5.90%
	Normal-weight	2246	16786	13.30%
	Overweight	2071	10390	19.90%
	Obese	3576	10403	34.30%
	Total	8047	40156	20.03%

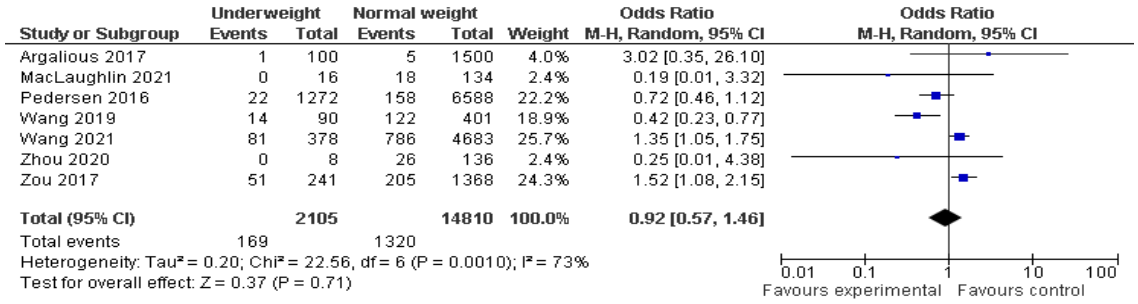

Figure 4a: AKI stage 2 and Underweight.

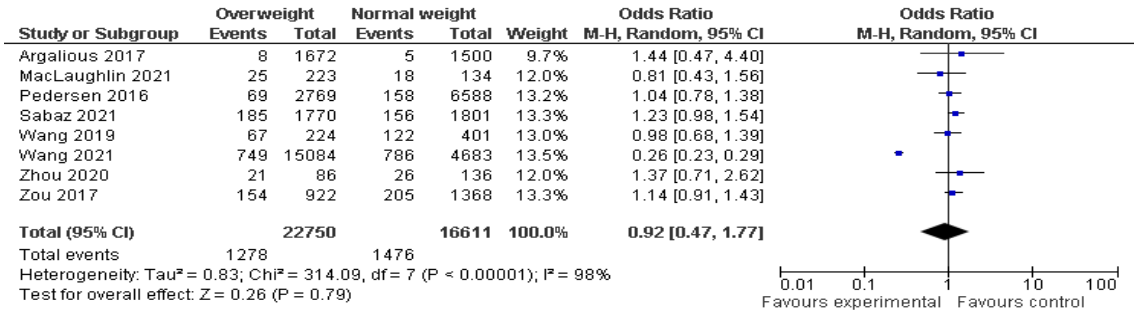

Figure 4b: AKI stage 2 and Overweight.

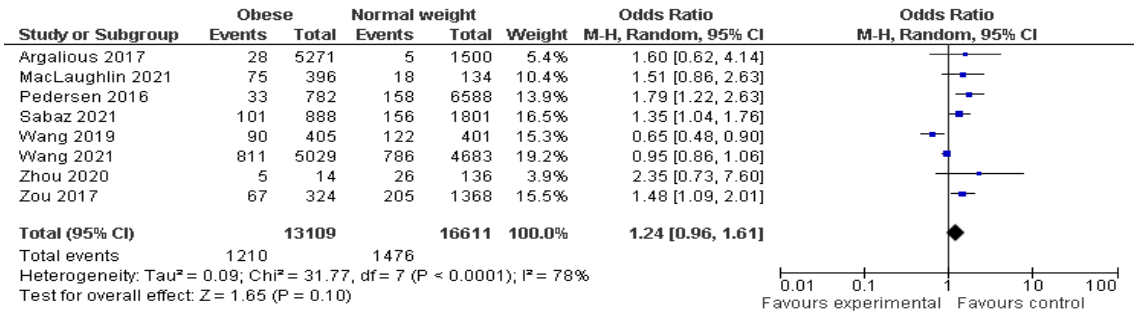

Figure 4c: AKI stage 2 and Obese.

BMI and AKI patients with clinical outcomes

BMI and AKI mortality: The study showed that underweight population were more likely to experience AKI mortality, OR was 1.44, 95% CI: 1.04 to 2.00, P=0.03. However, overweight and obese population which were less likely to be associated with AKI mortality, even it was statistically insignificant, ORs were 0.73, 95% CI: 0.53 to 1.01, P=0.05 and 0.71, 95% CI: 0.40 to 1.27, P=0.24 respectively. A minimal, and substantial heterogeneity with I^2=0%, P=0.46, I^2=22%, P=0.26, and I^2=82%, P=0.02 were found in underweight, overweight, and obese group respectively (Figure 7a-7c).

BMI and LOS in ICU: The pooled results of two included studies show that 31% of obese patients stay in ICU for a short period of time compared to normal-weight group, OR 0.69, 95% CI: 0.37 to 1.01, p=0.0001. Similarly, underweight (four studies) and overweight (three) group were also more likely to stay in ICU for short time compared to normal-weight, but it was no statistically significant, OR: 0.25, 95% CI: -0.86 to 1.36, p=0.66 and -1.0, 95% CI: -3.23 to 1.23, p=0.38, respectively. There was A minimal, and moderate heterogeneity with I^2=0%, P=0.84, I^2=9%, P=0.35, and I^2=58%, P=0.09 were found in obese underweight, and overweight group respectively (Figure 8a-8c).

BMI and LOS in hospital: Compared with normal weight group, findings of four included studies (statistically insignificant) reveal that 96% of underweight are not associated with LOS in hospital with OR of 0.04, 95% CI: -1.79 to 1.87, P=0.96. Moreover, results of three

Table 5: Incidence of AKI in sub-groups.

Sub-group	Event (AKI)	Total	Percentage
Underweight	429	2404	18%
Normal-weight	4184	16441	25.40%
Overweight	3064	10157	30.10%
Obese	2393	11412	21%
Overall total	10070	40414	24.90%

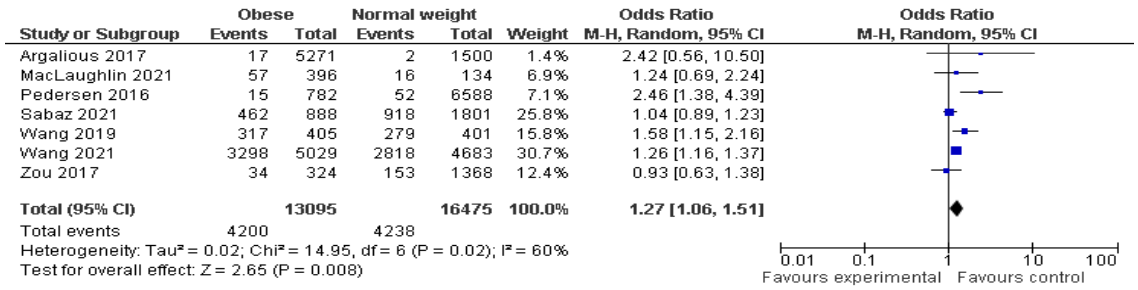

Figure 5a: AKI stage 3 and Obese.

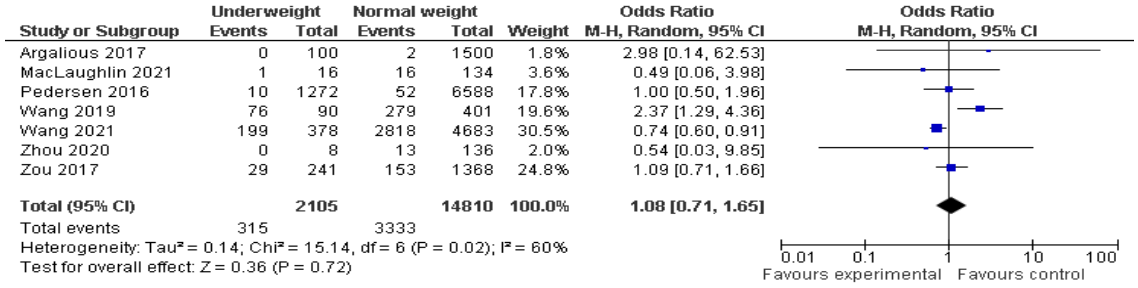

Figure 5b: AKI stage 3 and Underweight.

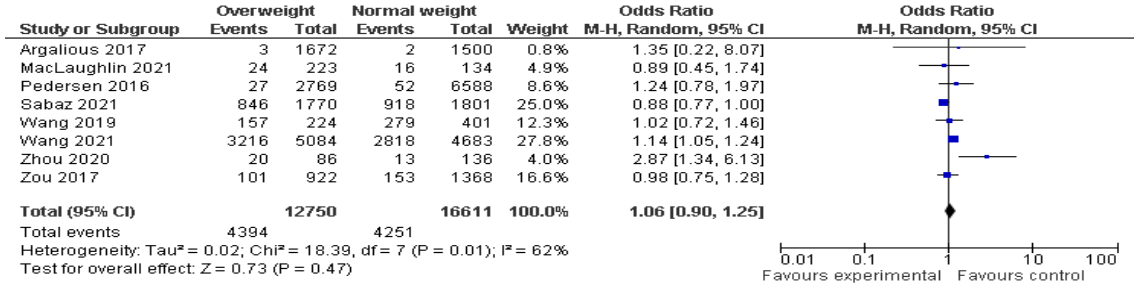

Figure 5c: AKI stage 3 and Overweight.

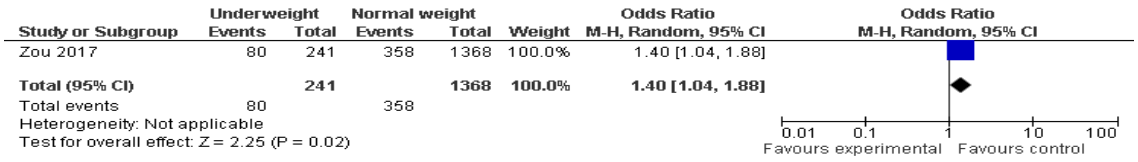

Figure 6a: AKI stage 2-3 and Underweight.

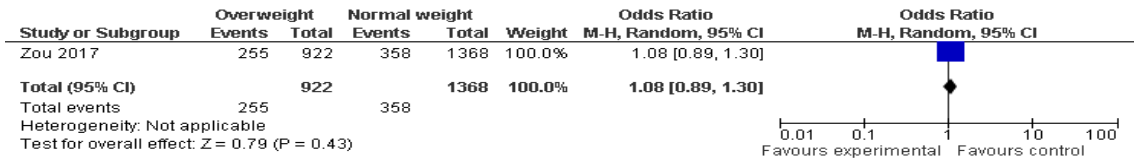

Figure 6b: AKI stage 2-3 and Overweight.

included studies show that 73% of overweight patients were less likely to stay in hospital for long time compared with normal-weight group, OR was 0.27, 95% CI: -0.83 to 1.38, P=0.63. However, two included studies show that there was no difference of LOS in hospital for obese group compared with normal-weight group, OR was 1.0, 95% CI: 0.62 to 1.38, P=0.0001. There was substantial, and minimal heterogeneity

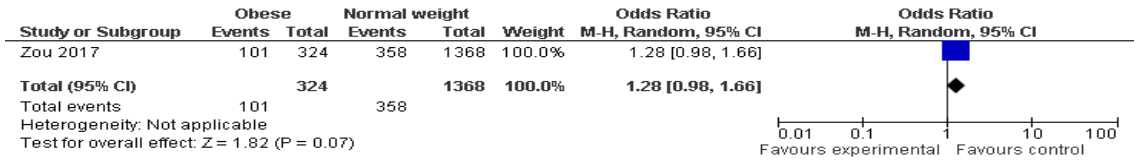

Figure 6c: AKI stage 2-3 and Obese.

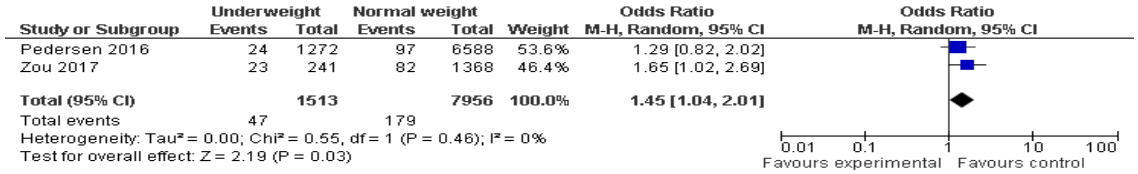

Figure 7a: AKI mortality and Underweight.

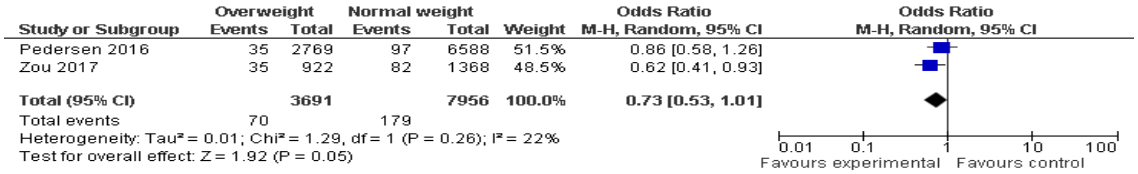

Figure 7b: AKI mortality and Overweight**.**

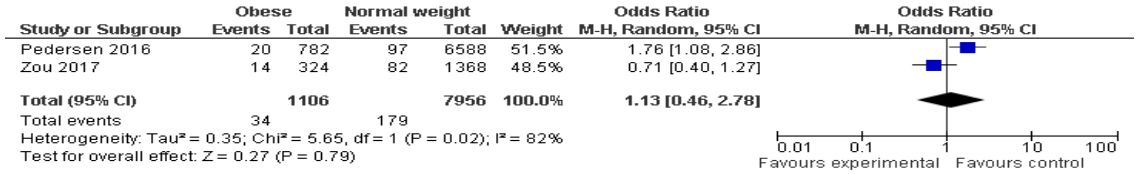

Figure 7c: AKI mortality and Obese.

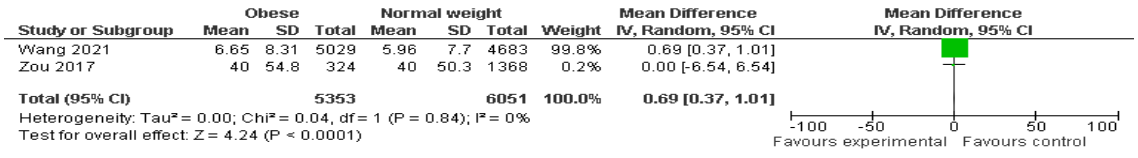

Figure 8a: LOS in ICU and Obese.

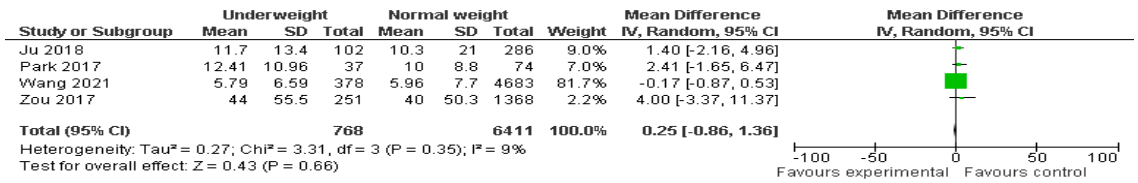

Figure 8b: LOS in ICU and Underweight.

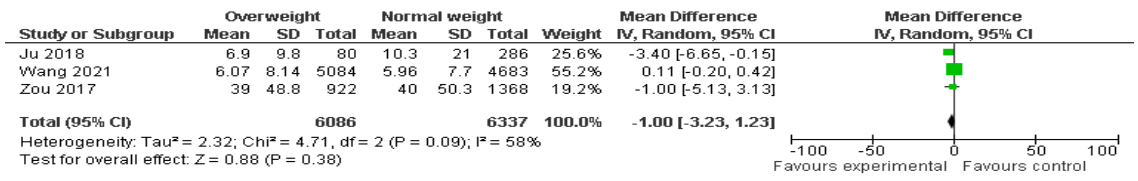

Figure 8c: LOS in ICU and Overweight.

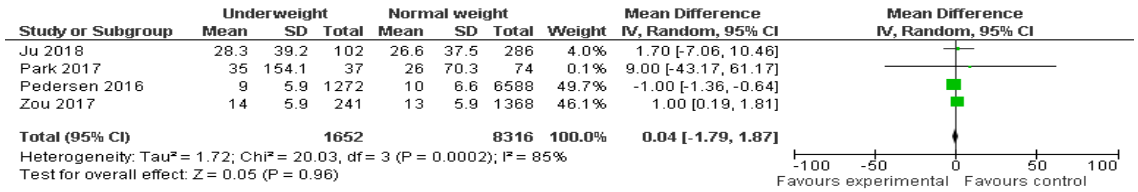

Figure 9a: LOS in Hospital and Underweight.

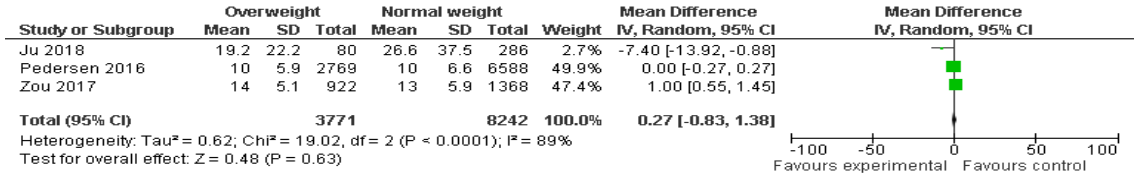

Figure 9b: LOS in Hospital and Overweight.

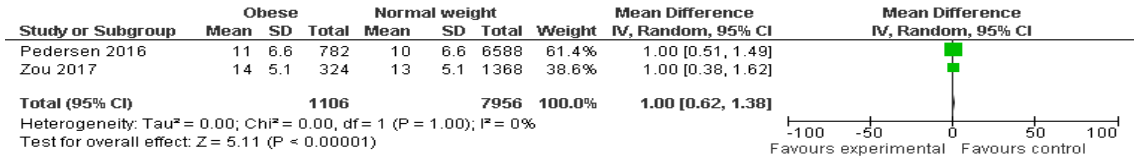

Figure 9c: LOS in Hospital and Obese.

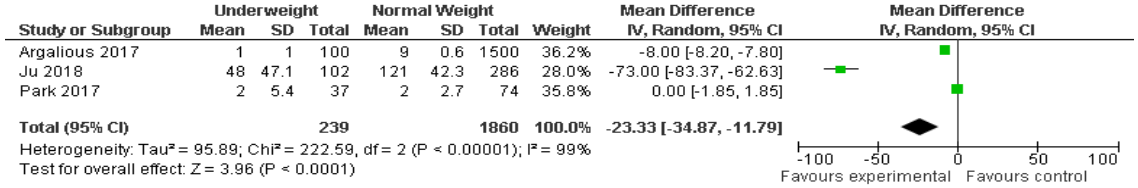

Figure 10a: Hospital mortality and Underweight.

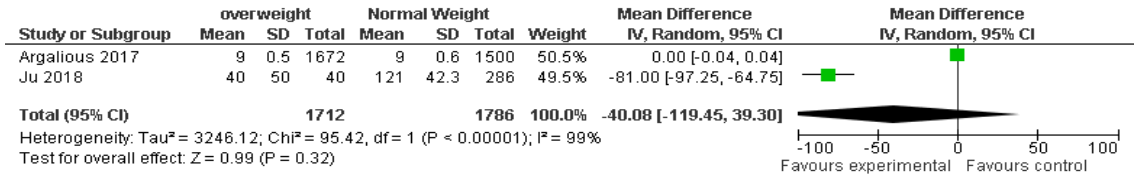

Figure 10b: Hospital mortality and Overweight.

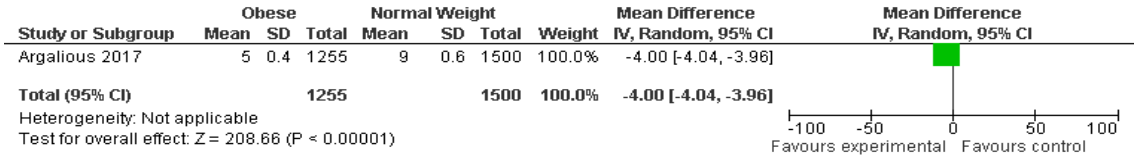

Figure 10c: Hospital mortality and Obese.

with I^2=85%, P=0.0002, I^2=89%, P=0.0001 and I^2=0%, P=1 were found in underweight, and overweight group respectively (Figure 9a-9c).

BMI and hospital mortality: Results from three included studies in underweight group and one study in obese group show that there were less associated with hospital mortality compared to normal weight group, OR was -23.33, 95% CI: -34.87 to -11.79, p=0.0001 and -4, 95% CI: -4.04 to -3.96, P=0.00001 respectively. There was considerable heterogeneity among these included cohorts

in underweight group with I^2=99%, P=0.0001. The findings from two included cohorts show that overweight was also less associated with hospital mortality, but not statistically significant, OR: -40.08, 95% CI: -119.45 to 39.30, P=0.32. The heterogeneity was considerable with I^2=99%, P=0.00001. There one study included in this meta-analysis showed that the number of hospital mortality in obese population was lesser compared normal weight group, OR: -4.0, 95% CI of -4.04 to -3.96, p=0.00001, heterogeneity is not applicable (Figure 10a-10c).

Discussion

Current review introduces the possibility of obesity paradox in AKI, where higher BMI is associated with AKI morbidity, while underweight group is associated with AKI mortality.

Based on the meta-analysis results, AKI incidence was 24.9% and higher AKI incidence in subgroup was 30.1% in overweight, while based systematic analysis, findings demonstrate that the highest incidence of AKI was 92.8% in obese group. These findings show that AKI incidence trend is associated with high BMI. AKI stages were not statistically associated with BMI, except AKI stage 2-3 was more likely to develop in underweight with OR of 1.4. Besides, AKI mortality rate was high in underweight group compared to normal-weight group, while high incidence was associated with elevated BMI. The current findings are in the line with a retrospective study with 11,736 participants conducted in Australia, where morbid obese and overweight patients were 2.9 1.4 times more likely to develop renal failure and morbidity respectively. The findings of this study found that AKI mortality was not associated with high BMI [34]. Moreover, a cohort study carried out in Denmark from 2005-2011 with 13,529 participants shows that 17.9% were obese patients while 11.9% were normal-weight, nevertheless, AKI mortality was 23.1%, 14.1%, 10.7%, 15.2% in underweight, normal-weight, overweight, and obese patients respectively [35].

Although the higher BMI is accompanied with low rate of AKI mortality, much caution could be taken as the current systematic review reveals that high BMI is associated with different comorbidities (hypertension and diabetes mellitus), where percentage of hypertension in overweight and obese was 31.1% and 46.2% respectively, which are high compared to underweight (19.9%). Moreover, percentage of diabetes mellitus in overweight and obese was 19.9% and 34.3% respectively, which is also high compared with underweight (5.9%). Based on these comorbidities, recent studies have shown that hypertension and diabetes mellitus are associated with AKI in overweight and obese patients. For instance, a retrospective study carried out in Poland with 215 patients shows that among 70% of patients with hypertension were associated with 85%, 75%, and 30% of post-renal AKI, renal AKI, and pre-renal AKI respectively [36]. Besides, Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) database was used to collect the data in the study enrolled 2162 neonates, where the overall AKI was 29.9% with the association of hypertension over 41.2% compared to 26.2% of control group [37]. Nevertheless, it has been shown that hemoglobin A1c more than 9% is associated with AKI with OR of 1.29, 95% CI: 1.18-1.41 up to 1.33, 95% CI: 1.13-1.57 compared with baseline A1c of 6-6.9% [38]. Moreover, a cohort study of 16,700 participants shows that 48.6% of diabetes patients versus 17.2% controls are more likely to develop AKI [39]. Based on these findings, there might be a great impact of diabetes and hypertension on AKI development. Therefore, more studies are welcomed to reveal the association between these comorbidities and AKI, and related cellular mechanism behind. Moreover, particularly to the current results, it will be interesting to understand why and how low BMI induces AKI mortality in future.

Altogether, the link of low BMI and mortality for patients with AKI shows a more clinically useful observation, therefore clinicians should be especially vigilant when managing AKI risk.

The study was challenged with different limitations. For instance, BMI can be affected by different factors like ethnicity which can increase the heterogeneity [40]. Besides, different sample sizes contribute to the different power of the study which affects the pooled result and result in the study heterogeneity.

Conclusion

Although high BMI is known to enhance the chronic kidney diseases, having a higher BMI might be associated with AKI morbidity, while low BMI might be associated with AKI mortality. More studies are recommended.

Declaration

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