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Risk factors for the development of delirium in elderly patients undergoing orthopaedic surgery: A systematic review and meta-analysis

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ABSTRACT

Objective. Delirium is a temporary neuropsychiatric syndrome characterized by fluctuations in cognition and attention. Delirium is one of the most common complications seen in old individuals after orthopaedic surgery. With a high incidence, the clinical picture of delirium increases the length of hospital stay and increases healthcare-related costs. This study has aimed to systematically review the national and international studies that investigated the risk factors leading to delirium in geriatric patients after orthopaedic surgery and to perform a meta-analysis using the data reported by those studies. *Materials and Methods*. A preliminary literature review was performed on six databases. The following English keyword combinations were used including 'Orthopaedic Surgery', 'Geriatrics', 'Elderly', and 'Delirium'. The results of trials were evaluated with random or fixed effect model according to the heterogeneity. Statistical evaluation was performed by using Comprehensive Meta Analysis version 3 programme. *Results*. The total sample size of the studies included in the analysis was 892. In geriatric patients; who had undergone orthopaedic surgery and developed delirium, the random-effects model revealed a high-level, in the positive direction, and statistically significant ($p<0.05$) overall effect size of 5.21 (CI; 1.33-20.33) for gender, 1.33 (CI; 0.58-2.06) for age, 11.30 (CI; 4.70-27.12 for polypharmacy, and a low-level, in the positive direction, and statistically significant ($p<0.05$) overall effect size of 0.12 (CI; 0.05-0.27) for mini-mental state examination as the risk factors leading to the development of delirium. *Conclusions*. Advanced age, female gender, polypharmacy, and a mini-mental state examination score of 17-23 are major risk factors for the development of delirium after orthopaedic surgery.

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Introduction

Postoperative delirium (POD) is defined as an acute neuropsychiatric syndrome characterized by a temporary and reversible functional brain disorder that manifests with sudden disturbances in consciousness and orientation resulting from physical or physiopathological factors after surgical interventions [1-3]. Although the physiopathology of delirium has not been fully clarified as yet, several hypotheses have been proposed. Of these hypotheses, disorders of cerebral oxidative metabolic processes and aberrations involving more than one neurotransmitter are the major ones [4-7]. The risk factors leading to delirium are examined in two separate groups. These groups are the predisposing risk factors and the risk factors that trigger delirium. The predisposing risk factors increase the tendency to develop delirium. Already existing at the time of hospital admission and acting on the susceptibility of the patient, these factors include male gender, fractures, depression, visual disturbances, dementia, polypharmacy, and age as the major ones. The risk factors that trigger delirium are those that trigger, facilitate, and lead to the development of delirium. Of these factors, surgical interventions, fluid-electrolyte disturbances, pain, invasive catheterization (CVP, indwelling urinary catheters, nasogastric intubation, etc.), medications (especially neuroleptics, narcotics, etc.); the use of hearing devices, eye-glasses, etc.; and the length of stay in the inpatient unit or the intensive care unit are some of the major ones [2,3].

Delirium is seen mostly in surgical clinics after intensive care units in hospitalized patients [6,7]. In the literature, it has been reported that the prevalence of delirium is 50% in hospitalized geriatric patients, and that 3-53% of patients undergoing major surgery and 83% of

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critical patients in intensive care are impacted by delirium [8,9]. Although many factors cause delirium, delirium is observed more commonly in some patient groups, primarily geriatric patients and patients undergoing cardiac and hip surgery [1,10]. Delirium can be seen in any age group in an age-dependent pattern. It has been reported in the literature that the incidence increases at the age of 60 years and older, and that 80 years of age is an important risk factor [5]. The relationship between advanced age and delirium is associated with the physiological and cognitive changes which occur with ageing. During the ageing process, changes also occur in the brain, similar to physiological alterations occurring in the heart, kidneys, the liver, and other organs. There is known to be a decline in the brain weight, the blood supply to the brain, the number of neurons, and the neurotransmitter quantities together with ageing [10,11]. Delirium has a negative effect not only on patients, but also on their relatives, and the healthcare system in emotional, functional, and financial aspects. These effects lead to several consequences including longer hospital stay, and increased mortality, morbidity, and hospital costs [12-14]. Cognitive and functional losses, which are the long-term effects of delirium, may continue further after the hospital discharge leading to rehospitalization [13,14]. Affecting wellbeing unfavorably, the clinical symptoms and risk factors of delirium have not yet been fully recognized and are often not identified by healthcare professionals as they can be misdiagnosed as other types of cognitive disorders [5, 15]. The aim of this study was to systematically review the national and international studies that have investigated the risk factors leading to delirium in geriatric patients after orthopaedic surgery and to perform a meta-analysis using the data reported by those studies. It can be considered that systematic reviews and meta-analyses for the investigation of risk factors of delirium will contribute to the literature, increase the awareness of healthcare professionals, and pave the way for future studies.

Materials and Methods

The type of the study, the study site, and the duration of the study

This study used the meta-analysis method, which is a quantitative study method. The study was carried out in the period from October 2019 to December 2019.

Ethical Requirements

The literature review model was used as this study is a meta-analysis study. As the literature review does not affect animals or humans directly, ethics committee approval was not sought.

Steps of the Study

The steps of the study were categorized based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement) and MOOSE (Meta-analysis of Observational Studies in Epidemiology) criteria concerning the papers to be included in the study. The articles meeting those criteria were identified and are presented in Figure1 and Table 1.

Detailed Literature Review

Using the selected keywords in English 'Orthopaedic Surgery, Geriatrics, and Delirium'; the literature review was performed on all of the planned databases. Relevant research articles published in the period from January 2010 to November 2019 were retrieved from CINAHL, ScienceDirect, Google Academics, Web of Science, PubMed, and Ovid and were included in the assessment process. After retrieving the relevant articles from each of these websites, any repetitions were excluded, before proceeding to the step of reading the article titles, abstracts, and full-text manuscripts [16-19].

A total of 346 articles were identified with the planned search strategy on the six databases. After excluding the repeated papers and those with non-relevant titles and abstracts, the remaining 282 papers were included in the assessment. The titles and abstracts were read to select the papers to be included in the full text-reading process. The articles with a non-relevant subject matter were categorized in detail and excluded from the study. The articles search and the elimination processes used in the selection of the papers to be included in the study are presented in Figure 1 [16,20,21].

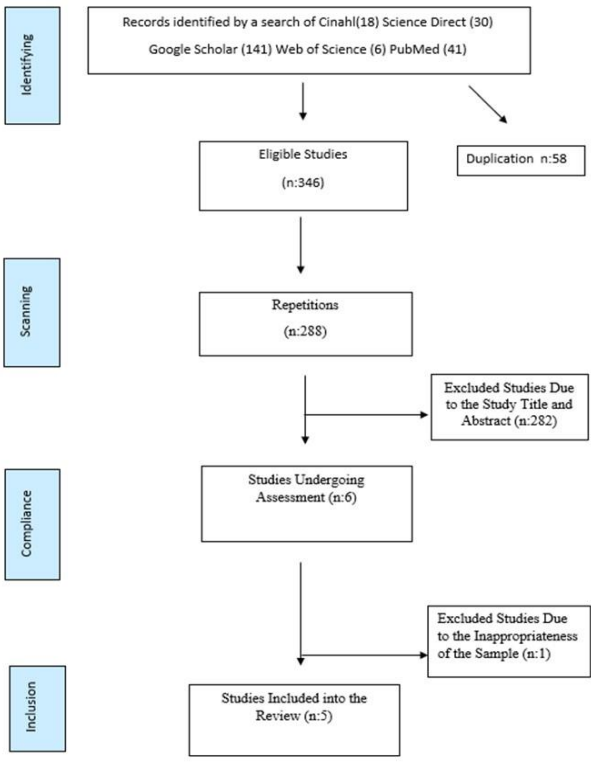

Figure 1. Study selection. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flowchart

Table 1. Characteristics of Studies Included in the Review

Study title	Study Objective	Assessment tools used in the study	Sample characteristics	Study outcomes
Approach to The Risk Of Delirium In An Orthogeriatric Unit Bert et al. 2019 [22]	The aim of this study was to determine the efficacious method between two different methods used for the management of delirium risk in an orthogeriatric unit.	The Confusion Assessment Method Scale	Orthogeriatric patients (N: 85). Cohort study	The experimental treatment was successful as the incidence of delirium was reduced and the reduction in the delirium duration was found to be statistically significant.
Relationship of Postoperative Delirium And Cognitive Impairment And Their Impact On Functional Status In Older Patients Undergoing Orthopaedic Surgery: A Prospective Cohort Study Liang et al. 2014 [19]	The aim of this study was to evaluate the post-discharge functioning of the patients developing delirium after orthopaedic surgery and to assess the relationship between postoperative delirium and underlying cognitive disorders.	Chinese Geriatric Depression Scale Activities of Daily Living Confusion Assessment Method Mini-Mental State Examination ASA Lawton-Brody instrumental ADL (IADL)	Old patients (N: 232) undergoing orthopaedic surgery. Cohort study	Early assessment of cognitive functional status is needed to improve the postoperative functional status of patients and prevent delirium after orthopaedic surgery. Postoperative delirium can be predicted by reductions in IADL scores.
Prevalence of delirium, risk factors, and cognitive functions in elderly hip fracture patients with general and spinal anesthesia Atay et al. 2012 [21]	The aim of this study was to investigate the prevalence of postoperative delirium in Turkey; developing after hip fractures in association with the presence of some risk factors and to evaluate the effects of anesthesia on postoperative cognitive functions.	Structured clinical interview scale based on DSM-IV Standardized Mini-Mental Test (SMMT) Delirium Rating Scale (DRS)	Old patients undergoing orthopaedic surgery (N:70). Descriptive study	A history of previous delirium and advanced age are unpreventable risk factors. Supportive treatment for metabolic disturbances in hip fracture patients may reduce the risk of postoperative delirium. However, it was determined that the type of anesthesia was not a risk factor for predisposing to delirium and cognitive impairment in the postoperative period.
Unraveling the Relationship Between Delirium, Brain Damage, and Subsequent Cognitive Decline in a Cohort of Individuals Undergoing Surgery for Hip Fracture. Beishuizen et al. 2017 [20]	To evaluate the relationship between serum S100B levels (a marker of brain injury), delirium, and subsequent cognitive decline.	Informant Questionnaire on Cognitive Decline Short Form Mini-mental state examination S100B levels in serum samples	Patients, who were 65 years and older (65-102 years), and who were admitted for hip fracture surgery (n = 385). Descriptive study	Serum S100B levels were not correlated with developing delirium in a cohort of old patients with hip fractures. S100B was associated with cognitive decline or death in the first year after hip fracture only in participants without perioperative delirium. S100B appears to have limited value as a biomarker of delirium-related brain injury.
Comparison of incidence and risk factors of delirium between general and regional anesthesia in elderly patients after lower extremity surgery Kupeli et al. 2016 [5]	The aim of this study was to compare the risk factors and delirium incidence in the postoperative period in old patients undergoing orthopaedic surgery under general or regional anesthesia.	Confusion Assessment Method Delirium Rating Scale-Revised-98	Old-age patients (N:120) at the age of ≥65 years; for whom total hip or knee arthroplasty and femoral fracture surgery were scheduled. Descriptive study	We found that the incidence of delirium was 12.5% in old-age patients, who underwent total hip or knee arthroplasty and femoral fracture surgery. Advanced age and polypharmacy are the risk factors for delirium. Delirium increases the length of hospital stays and costs.

Study Search and Inclusion criteria for the Meta-analysis

i. Studies presented in original papers,

ii. Papers in English or Turkish

iii. Relevant papers published in national/international peer-reviewed journals accessible by the university as an institution,

iv. Papers of studies which included patients aged 65 years and older who were diagnosed with delirium after orthopaedic surgery,

v. Papers presented over the last 9 years (2010-2019).

vi. The full-text papers reporting the total participant numbers in the groups and reporting the changes in the predetermined study outcomes completely and quantitatively were included in the present study.

vii. Patients with no history of delirium or dementia before the surgical intervention,

viii. Patients with no history of neurological or mental disorders,

The Review, Coding, and the Methodological Quality Assessment of the Papers as per the Inclusion Criteria

Independent and detailed readings of abstracts and full-text manuscripts of the papers were completed by two researchers/specialists to prevent publication bias. The papers included in the assessment were coded according to descriptive characteristics, as follow:

i. The title and the date of the study
ii. The type and the objective of the study
iii. The sample size of the study
iv. Whether the study was interventional
v. The scales used in the study
vi. The primary outcome of the study
vii. The quality assessment score

After examining the selected articles, 12 criteria proposed by Polit and Beck for assessing the quality of the research were used for the remaining six studies [17]. These criteria allow for an overall assessment of the objectives, sample characteristics, findings, and results of the studies. Each of these selected studies was assessed by the two researchers independently using all of the criteria. A score of '1' or '0' was assigned for each criterion according to whether or not the specified paper met the criteria. The total score that could be attributed to one paper ranged from 0 to 12. All papers with study subgroups were assessed by two researchers independently. A paper was considered eligible if a score of 7 or more was attributed after the quality assessment. Of the studies (n=9) which were assessed for quality by the independent raters, three were considered 'weak' and one was considered 'moderate'. As it was planned to include only the 'strong-quality' and 'moderate-quality' studies in the meta-analysis, 6 studies meeting those quality criteria were identified. However, one of these six studies was then excluded as it was not found suitable for inclusion in the meta-analysis due to the sample size exceeding the maximum levels and would therefore prevent the calculation of the effect size. Thus, 5 studies were included in the meta-analysis. The quality assessment of the 5 studies included in the meta-analysis and the distribution of scores attributed to each field are presented in Table 1.

Assessment of the Primary Outcomes

In the papers included in the study, the assessments and analyses were performed based on the comparisons of the delirium incidence rate, age ranges, the number of risk factors and polypharmacy, gender distribution in the sample, the use of evaluation scales for diagnosing delirium, and the scores obtained from those scales between the groups developing delirium and the groups without delirium. As the studies did not have a randomized controlled design, descriptive analyses were included in the study.

Data Analysis

'Comprehensive Meta-Analysis Academic/Non-profit Pricing (Version 3)' was used as the licensed software for the data analysis. The data reported in all of the papers meeting the inclusion criteria and included in the study were entered into the CMA software, and the papers were assessed for heterogeneity. The effect sizes, study weights, 95% confidence intervals, and the overall effect size of all studies were calculated using the random effects model or the fixed effects model based on the p-values of ≤ 0.05 or >0.05 respectively, which resulted from the heterogeneity tests in the analysis of the groups. The 'RR' and 'OR' values were primarily used to evaluate the overall effect size in the analysis of the binary data. The statistical significance limit was accepted as $p \leq 0.05$ for the assessment of the overall effect. A funnel plot was performed to test the publication bias, and the results obtained in the calculations of the classic fail-safe N and Tau coefficients were used.

Results

Descriptive Results

Of the studies included in the meta-analysis, one was a descriptive study and the remaining four were cohort studies, all published between 2010 and 2019. Each of these five studies was published in one of the following years; 2012, 2014, 2016, 2017, and 2019. The oldest study was published in 2012.

Characteristics of the Study Samples in the Studies Included in the Assessment, and the Therapeutic Areas on which the Studies were Conducted.

A total sample size was determined of 892 patients aged 65 years and older. The size of the sample in each study

included in the meta-analysis ranged from 70 – 385. In the study by Kupeli et al (2016) included in the meta-analysis, the mean age was 71.8 ± 6.7 years in the control group and 72.7 ± 6.1 years in the patient group [5,18]. There were no statistically significant differences between the groups (p = 0.486). The percentage of female patients was 69.1% and the percentage of male patients was 30.9%. A total of 46 patients underwent hip arthroplasty, 65 patients underwent knee arthroplasty, and 9 patients underwent other types of surgery for limb amputation, treatment of fractures, and tumors. In the study by Liang et al. (2014), all patients who were scheduled to undergo orthopaedic surgery with a mean age of 74.7 ± 7.8 years were included [19]. Of those patients, 46.6% were males and 63.4% were females, 25.9% underwent scheduled spinal surgery, 43.1% knee surgery, 17.7% hip arthroplasty, and 13.4% open reduction and internal fixation. In the study by Beishuizen et al. (2017), the study population comprised 32.3% males and 77.7% females with a mean age of 86.7±6.5 years, all of whom underwent surgery for hip fracture [20]. Atay et al. (2012), reported on a sample of 54.3% females and 45.7% males with a mean age of 75.03 ± 9.82 years, hospitalized for surgical treatment of a hip fracture [21]. The study by Bert et al. (2019) included 75% females and 25% males with a mean age of 85 years, all of whom underwent surgery for femoral fractures [22].

Questionnaires and Scales used in the Studies Included in the Assessment

In addition to the DSM criteria, several types of scales have been developed to screen and diagnose delirium and to determine the severity [23,24]. These scales are the confusion assessment method for the ICU (CAM-ICU), the intensive care delirium screening checklist (ICDSC), the NEECHAM confusion scale, the nursing delirium screening scale (Nu-DESC), and the delirium detection score (DDS) [25-29]. Of those evaluation tools, the most commonly studied ones are CAM-ICU and ICDSC and the most commonly used one is CAM-ICU. Of the studies included in the present meta-analysis, Bert et al. (2019) and Kupeli et al. (2016) used the confusion assessment method to assess the cognitive status of the patients [5,22]. Beishuizen et al. (2017) used the informant questionnaire on cognitive decline-short form and the mini-mental state examination (MMSE) [20,25-29]. Atay et al. (2012) used the standardized mini-mental test [21]. Liang et al. (2014) administered the Chinese geriatric depression scale, activities of daily living, confusion assessment method, MMSE, the American Society of Anaesthesiologists physical status classification (ASA), and the Lawton instrumental activities of daily living (IADL) scale [19]. For delirium screening and rating, Kupeli et al. used the Delirium Rating Scale-Revised-98 version, Atay et al. used the delirium rating scale (DRS), and Beishuizen et al. investigated S100B in blood serum samples [5,18-22].

Risk Factors Leading to Delirium and Delirium Development in the Studies Included in the Assessment

The incidence of postoperative delirium after orthopaedic surgery was seen to range from 9.1-34.11%. The risk factors commonly evaluated in all of the studies were found to be age, gender, polypharmacy, and delirium assessment scale scores. The data of those risk factors were analyzed in the present study.

Methodological Quality Assessment

In the present study, the inter-rater agreement between the researchers was found to be 81% based on the quality assessment score. The reliability analysis revealed that Cohen's kappa was 0.84, which was within the 95% confidence interval [Confidence Interval (CI): 0.767-0.873]. Kappa values of <0 indicate poorer agreement than expected by chance, values in the range between 0.01 - 0.20 indicate negligible agreement, 0.21 - 0.40 indicate slight agreement, 0.41 - 0.60 indicate moderate agreement, 0.61 - 0.80 indicate substantial agreement, and values in the range of 0.81 - 1.00 indicate perfect agreement (8), or values of ?0.75 indicate excellent, 0.40-0.75 indicate moderate-good, and values less than 0.40 are considered poor agreement [9]. The kappa value of 0.82 in the present study indicates perfect inter-rater agreement. The mean scores attributed to each study by the investigators are presented in Table 1.

Results of the Analysis

In geriatric patients; who had undergone orthopaedic surgery and developed delirium, the following high-level, in the positive direction, and statistically significant overall effect size of 5.21 (CI; 1.33-20.33; p <0.05) was found for gender, 1.33 (CI; 0.58-2.06; p 0.05) was found for age, and 11.30 (CI; 4.70-27.12; p 0.05) was found for polypharmacy, and the following low-level, in the positive direction, and statistically significant overall effect size of 0.12 (CI; 0.05 -0.27; p 0.05) was found for MMSE as the risk factors leading to the development of delirium. A forest plot chart was used to present the results of the meta-analysis of gender, age, polypharmacy, and the delirium screening scores in the five included studies.

- *Gender*

The heterogeneity test for the gender variable as a risk factor of delirium yielded a p-value of < 0.05 and a Q-value (29.509) of more than the corresponding df value revealing a heterogeneous construct (Table 2). The statistical I2 value was calculated as 86.44. As a result of the calculations, the study effect sizes for gender were evaluated according to the random effects model.

The random effects analysis showed that the overall effect size of gender on the development of delirium was at a high-level, positive, and statistically significant with a value of 5.21 (CI: 1.33-20.33; p<0.05). Forest plot of analysis for gender is shown in Figure 2. Female gender was found to play a more significant role compared to male gender as a major risk factor for the development of delirium.

Table 2. Heterogeneity Test Results for The Gender, Age, Polypharmacy And Delirium Screening Score Variables

	Effect size and 95% interyal				Test of null (2-Tail)		Heterogenity				Tau-squared			
Variable	**Number Studies**	**Point estimate**	**Lower limit**	**Upper limit**	**Z-value**	**P-value**	**Q-value**	**df (Q)**	**P-value**	**I-squared**	**Tau Squared**	**Standard Error**	**Variance**	**Tau**
Gender	5	5.425	3.283	8.964	6.600	0.000	29.357	4	0.000	86.374	2.083	1.708	2.916	.,443
Age	5	0.899	0.729	1.070	10.343	0.000	51.866	4	0.000	92.288	0.630	0.562	0.316	0.794
Polypharmacy	3	11.300	4.708	27.127	5.427	0.000	0.230	2	0.891	0.000	0.000	0.762	0.581	0.000
Delirium screening score	3	0.125	0.081	0.192	-9.419	0.000	13.987	4	0.007	71.402	0.000	0.762	0.581	0.000

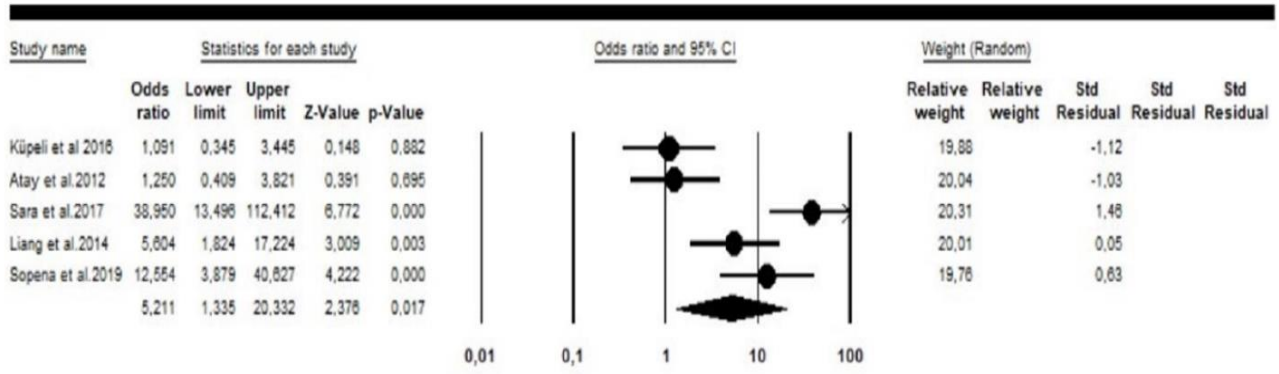

Figure 2. Forest plot of analysis for gender

o *Age*

The heterogeneity test yielded a p-value of < 0.05 and Q-value (51.866) more than the corresponding df value (Table 2). The examination of the included studies in the meta-analysis for the age variable as a risk factor for delirium showed that the studies had a heterogeneous construct.

The statistical value I2 was calculated as 92.28. As a result of the calculations, the distribution of the effect sizes was evaluated using the random effects model. Female gender was found to play a more significant role compared to male gender as a major risk factor for the development of delirium.

According to the analysis carried out according to the random effects model, the overall effect size of age on delirium development was found to be 1.33 (CI: 0.58-2.06; p <0.05) as a high value with a positive direction and statistical significance. Forest plot of analysis for age is shown in Figure 3. This observed effect was higher especially in patients aged ≥75 years compared to patients ≤74 years and the risk for delirium was seen to increase with increasing age.

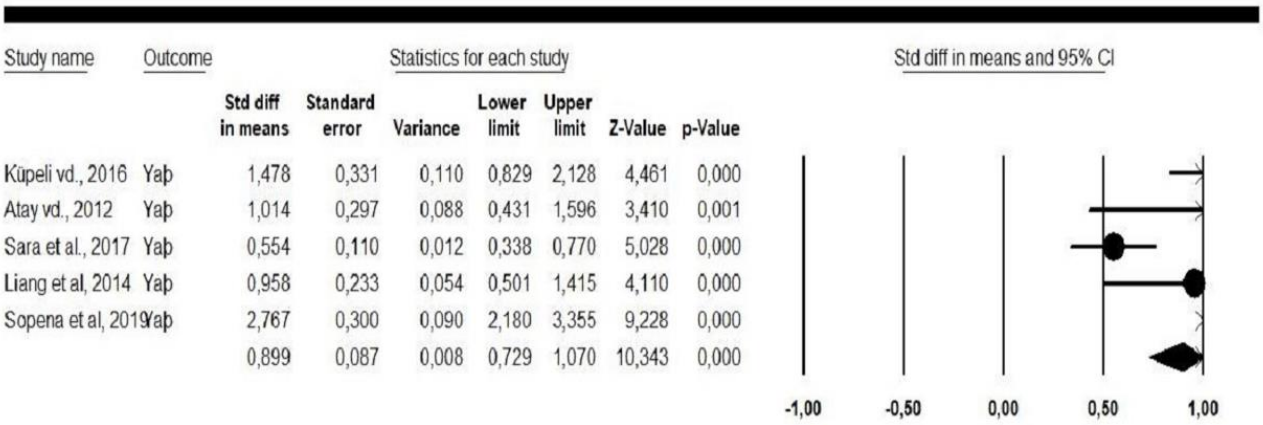

Figure 3. Forest plot of analysis for age

o *Polypharmacy*

The heterogeneity test yielded a p-value of >0.05 and Q-value (0.230) less than the corresponding df value (Table 2). The meta-analysis of the included studies showed that the studies examined for the polypharmacy variable as a risk factor for delirium had a homogeneous

construct. The statistical I2 value was calculated to be 0.000. As a result of the calculations, the effect size distributions were evaluated using the fixed effects model.

According to the analysis carried out according to the fixed effects model, the overall effect size of polypharmacy on developing delirium was 11.30 (CI: 4.70-27.12; p <0.05) and it was found to be at a high level with a positive direction and statistical significance. Forest plot of analysis for polypharmacy is shown in Figure 4. This effect was determined to be higher in patients using three or more types of drugs compared to patients using fewer than three drugs concurrently and the risk of delirium increased as the number of medications increased.

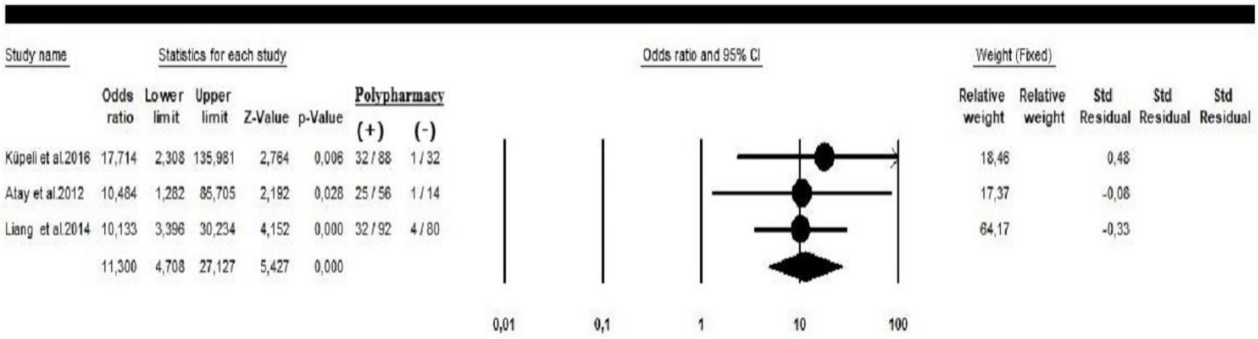

Figure 4. Forest plot of analysis for polypharmacy

o *Delirium Screening Score*

The heterogeneity test yielded a p-value of < 0.05 and a Q-value (13.937) more than the corresponding df value. The meta-analysis of the included studies for the delirium screening score variable as a risk factor for delirium showed that the examined studies had a heterogeneous construct. The statistical value of I2 was 0.611. As a result of the calculations, the effect size distributions were evaluated according to the random effects model. According to the results of the analysis carried out using the random effects model for the heterogeneity test to investigate the delirium screening score variable, the overall effect size of the MMSE scores on developing delirium was found to be 0.12 (CI: 0.05-0.27; p <0.05) at a low level and with a positive direction and statistical significance. Forest plot of analysis for delirium screening score is shown in Figure 5. Compared to patients with MMSE scores of 24-30, especially in patients with MMSE scores of 17-23, the observed effect was higher, and the risk of delirium increased as the MMSE scores decreased.

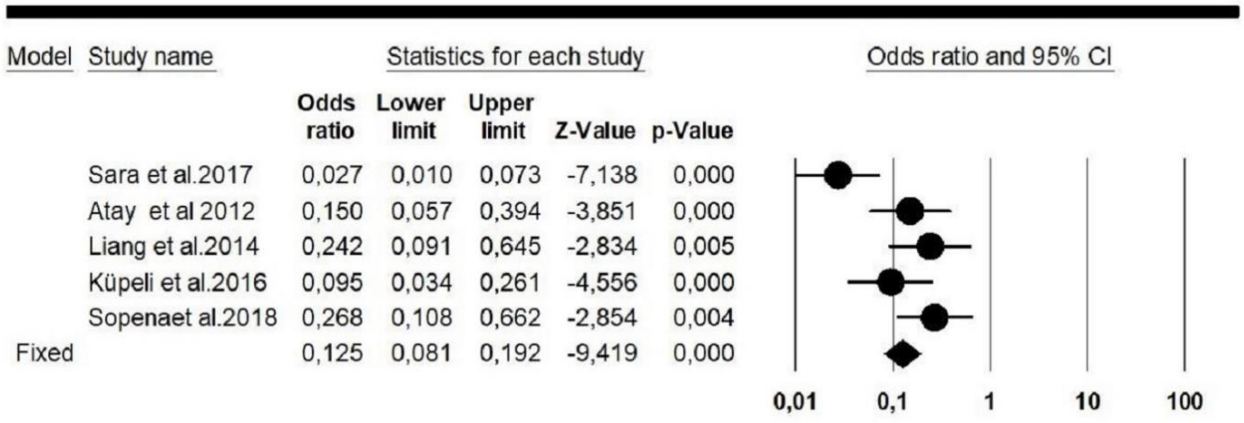

Figure 5. Forest plot of analysis for delirium screening score

In the studies examined within the scope of this research, the type of surgery, whether hip or knee surgery, was not determined to play a moderator role (Qb = 3.58; p> 0.05). Performing the surgical intervention either in the hip (r = 0.39) or the knee (r = 0.36) changed the effect size of the relationship between developing delirium and the risk factors of gender, age, polypharmacy, and delirium screening scores.

Publication Bias

The funnel scatter plot is considered a demonstration of the possibility of the publication bias. In the funnel scatter plot, the standard error values of the included studies are shown on the y-axis and the effect size is shown on the x-axis. Studies with small standard error values are scattered towards the top of the funnel shape and close to the average effect size. The studies with a large standard error value

scatter towards the bottom of the Figure 5. In the absence of any publication bias, the studies are expected to scatter symmetrically on both sides of the vertical line showing the combined effect size [29].

We could not observe publication bias according to funnel plots for the variables that we analyzed. Another way to determine the publication bias in meta-analysis research is to calculate Kendall's tau-b coefficient. In the absence of any publication bias, this coefficient is expected to be close to 1 and the double-tailed p-value is expected to be greater than 0.05 not indicating a significant difference [30]. According to the results of this statistical analysis (Kendall's tau-b=1.09; p=0.512), publication bias was not detected in the studies included in this meta-analysis.

Discussion

Delirium is a cognitive disorder commonly seen in elderly patients who undergo orthopaedic surgery, and results in a longer hospital stay with direct effects on morbidity and mortality rates. It has been previously reported that preoperative presence of cognitive impairment is one of the major risk factors for postoperative delirium after hip fracture surgery [31].

Another study, which aimed to predict the development of delirium during the preoperative care of orthopaedic surgery patients, found that patients with MMSE scores of ≤23 had a higher risk of developing postoperative delirium [32]. In this meta-analysis, patients with MMSE scores of 17-23 were seen to be at greater risk than those who scored 24-30.

Previous studies investigating postoperative delirium in adult patients have reported that polypharmacy could precipitate delirium and is an independent risk factor [33, 34]. In this meta-analysis, polypharmacy, especially when three or more drugs were used, was found to be a risk factor for the development of delirium.

In a study of elderly patients scheduled to undergo major orthopaedic surgery, male gender was reported to be a risk factor for delirium [35,36]. However, another study could not determine any significant effects of the gender variable on delirium [37]. In this meta-analysis, the effect of gender on precipitating delirium was significant, with female gender in particular showing a greater effect as a risk factor.

A study of adult intensive care patients reported old age as a risk factor for developing delirium [34]. Other studies on elderly patients in the postoperative period also reported that advanced age was a risk factor for delirium [38,39]. In this meta-analysis, age >75 years was observed to be a risk factor for the development of delirium after surgery.

It has been reported that the administration of a multi-factor intervention program based on care and supportive treatment in geriatric hip fracture patients starting from the time of admission reduced the incidence of delirium at admission from 34% to 22% [32].

It may not be possible to completely prevent the development of delirium in patients. However, a comprehensive evaluation of the patient can allow for the identification of high-risk patients and any further deterioration of the patient may be prevented [40,41].

The level of evidence of the development of postoperative delirium in elderly patients after orthopaedic surgery is quite limited throughout the world. Almost all of the studies have attempted methods to prevent delirium, but no studies could be found which have reported only the risk factors. Despite several available tools for the assessment of cognitive functions, no comprehensive tools have been developed to include all types of risk assessments in order to predict the emergence of delirium. Furthermore, studies have continued to stress the inadequacies of the incomplete information and practice reported in the literature for the use by health personnel working in the field and for the early recognition of delirium [5,15]. In addition to the MMSE examined in this study, several major dementia screening and rating scales are in current use, including IADL, Blessed Dementia Rating Scale- Consortium to Establish a Registry for Alzheimer's Disease (BDRS-CERAD), physical self-maintenance scale (PSMS), and the Katz index of independence in activities of daily living.

As dementia is a medical syndrome, collaboration with the psychiatry team and clinical evaluation are critical for the diagnosis. It will be more beneficial to remember the importance of collaboration and the importance of the clinical evaluation in addition to the use of the dementia screening and rating scales. The significance of the clinical evaluation and collaboration with psychiatry should be recognized in comorbid conditions of dementia and delirium and in conditions, where making a differential diagnosis is difficult.

Conclusions

Considering that delirium is an important cognitive problem throughout the world, it can be considered that this meta-analysis, which was conducted to identify the delirium risk factors and contribute to the provision of care and treatment in delirium, will pave the way for future studies. Within this scope, there can be seen to be a clear need for experimental studies, especially those providing adequate levels of evidence about this particular subject matter.

Orthopaedic surgery patients should be evaluated for delirium in the early postoperative period, associated risk factors should be identified, and prevention strategies should be developed. Based on the common risk factors identified in the present meta-analysis, an assessment scale can be developed to predict the development of delirium in the postoperative period.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

References

1. Martinez F, Tobar C, Hill N. Preventing delirium: should non-pharmacological, multicomponent interventions be used? A systematic review and meta-analysis of the literature. *Age Ageing*. 2015 Mar;44(2):196-204. doi: 10.1093/ageing/afu173
2. Chu Z, Wu Y, Dai X, Zhang C, He Q. The risk factors of postoperative delirium in general anesthesia patients with hip fracture: Attention needed. *Medicine (Baltimore)*. 2021 Jun 4;100(22):e26156. doi: 10.1097/MD.0000000000026156
3. Oh ES, Leoutsakos JM, Rosenberg PB, Pletnikova AM, Khanuja HS, Sterling RS, Oni JK, Sieber FE, Fedarko NS, Akhlaghi N, Neufeld KJ. Effects of Ramelteon on the Prevention of Postoperative Delirium in Older Patients Undergoing Orthopedic Surgery: The RECOVER Randomized Controlled Trial. *Am J Geriatr Psychiatry*. 2021 Jan;29(1):90-100. doi: 10.1016/j.jagp.2020.05.006
4. Hshieh TT, Fong TG, Marcantonio ER, Inouye SK. Cholinergic deficiency hypothesis in delirium: a synthesis of current evidence. *J Gerontol A Biol Sci Med Sci*. 2008 Jul;63(7):764-72. doi: 10.1093/gerona/63.7.764
5. Kupeli N, Leavey G, Moore K, Harrington J, Lord K, King M, Nazareth I, Sampson EL, Jones L. Context, mechanisms and outcomes in end of life care for people with advanced dementia. *BMC Palliat Care*. 2016 Mar 10;15:31. doi: 10.1186/s12904-016-0103-x
6. Jordan WJ. Mental Health & Drugs; A Map the Mind. *J Mind Med Sci*. 2020;7(2):133-140. doi: 10.22543/7674.72.P133140
7. Whitlock EL, Vannucci A, Avidan MS. Postoperative delirium. *Minerva Anestesiol*. 2011 Apr;77(4):448-56.
8. Cerejeira J, Firmino H, Vaz-Serra A, Mukaetova-Ladinska EB. The neuroinflammatory hypothesis of delirium. *Acta Neuropathol*. 2010 Jun;119(6):737-54. doi: 10.1007/s00401-010-0674-1
9. Sanders RD, Pandharipande PP, Davidson AJ, Ma D, Maze M. Anticipating and managing postoperative delirium and cognitive decline in adults. *BMJ*. 2011 Jul 20;343:d4331. doi: 10.1136/bmj.d4331
10. Holroyd-Leduc JM, Khandwala F, Sink KM. How can delirium best be prevented and managed in older patients in hospital? *CMAJ*. 2010 Mar 23;182(5):465-70. doi: 10.1503/cmaj.080519
11. Meyer M, Götz J, Parik L, Renkawitz T, Grifka J, Maderbacher G, Kappenschneider T, Weber M. Postoperative delirium is a risk factor for complications and poor outcome after total hip and knee arthroplasty. *Acta Orthop*. 2021 Oct 5:1-6. doi: 10.1080/17453674.2021.1980676
12. Morandi A, Jackson JC, Ely EW. Delirium in the intensive care unit. *Int Rev Psychiatry*. 2009 Feb;21(1):43-58. doi: 10.1080/09540260802675296
13. Tudorachi NB, Eva I, Dascalu CG, AL-Hiary R, Barbieru B, Paunica M, Motofei C, Moraru AC. The influence of serum calcium and magnesium levels in the radiological evolution of knee osteoarthritis. *J Mind Med Sci*. 2020;7(2):217-226. doi: 10.22543/7674.72.P217226
14. van Eijk MM, Slooter AJ. Delirium in intensive care unit patients. *Semin Cardiothorac Vasc Anesth*. 2010 Jun;14(2):141-7. doi: 10.1177/1089253210371495
15. Bramley P, McArthur K, Blayney A, McCullagh I. Risk factors for postoperative delirium: An umbrella review of systematic reviews. *Int J Surg*. 2021 Sep;93:106063. doi: 10.1016/j.ijsu.2021.106063
16. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009 Aug 18;151(4):264-9, W64. doi: 10.7326/0003-4819-151-4-200908180-00135
17. Papatheodorou SI, Evangelou E. Umbrella Reviews: What They Are and Why We Need Them. Methods *Mol Biol*. 2022;2345:135-146. doi: 10.1007/978-1-0716-1566-9_8
18. Küpeli İ, Güleç E, Biricik E, Biçer Ö, Güneş Y., Comparison of incidence and risk factors of delirium between general and regional anesthesia in elderly patients after lower extremity surgery. *Cukurova Med J*. 2016;41(1):34-40. doi: 10.17826/cutf.147304
19. Liang CK, Chu CL, Chou MY, Lin YT, Lu T, Hsu CJ, Chen LK. Interrelationship of postoperative delirium and cognitive impairment and their impact on the functional status in older patients undergoing orthopaedic surgery: a prospective cohort study. *PLoS One*. 2014 Nov 17;9(11):e110339. doi: 10.1371/journal.pone.0110339
20. Beishuizen SJ, Scholtens RM, van Munster BC, de Rooij SE. Unraveling the Relationship Between Delirium, Brain Damage, and Subsequent Cognitive Decline in a Cohort of Individuals Undergoing Surgery for Hip Fracture. *J Am Geriatr Soc*. 2017 Jan;65(1): 130-136. doi: 10.1111/jgs.14470
21. Atay IM, Aslan A, Atay T, et al. Prevalence of delirium, risk factors and cognitive functions in elderly hip

fracture patients with general and spinal anesthesia. *Turk Geriatri Dergisi*. 2012;15(3):273–78.

22. Sopena Bert E, Qanneta R, Valentí Moreno V, San José Laporte A. Aproach to the risk of delirium in an orthogeriatric unit. *Med Clin (Barc).* 2019 Apr 18;152(8):298-302. doi: 10.1016/j.medcli.2018.06.025
23. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, Davidson JE, Devlin JW, Kress JP, Joffe AM, Coursin DB, Herr DL, Tung A, Robinson BR, Fontaine DK, Ramsay MA, Riker RR, Sessler CN, Pun B, Skrobik Y, Jaeschke R; American College of Critical Care Medicine. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med.* 2013; 41(1):263-306. doi: 10.1097/CCM.0b013e3182783b72
24. Heymann A, Radtke F, Schiemann A, Lütz A, MacGuill M, Wernecke KD, Spies C. Delayed treatment of delirium increases mortality rate in intensive care unit patients. *J Int Med Res*. 2010 Sep; 38(5):1584-95. doi: 10.1177/147323001003800503
25. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med.* 1990 Dec 15;113(12):941-8. doi: 10.7326/0003-4819-113-12-941
26. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. *Intensive Care Med*. 2001 May;27(5):859-64. doi: 10.1007/s001340100909
27. Neelon VJ, Champagne MT, Carlson JR, Funk SG. The NEECHAM Confusion Scale: construction, validation, and clinical testing. *Nurs Res.* 1996 Nov; 45(6):324-30. doi: 10.1097/00006199-199611000-00002
28. Gaudreau JD, Gagnon P, Harel F, Tremblay A, Roy MA. Fast, systematic, and continuous delirium assessment in hospitalized patients: the nursing delirium screening scale. *J Pain Symptom Manage.* 2005;29(4):368-75. doi: 10.1016/j.jpainsymman.2004.07.009
29. Otter H, Martin J, Bäsell K, von Heymann C, Hein OV, Böllert P, Jänsch P, Behnisch I, Wernecke KD, Konertz W, Loening S, Blohmer JU, Spies C. Validity and reliability of the DDS for severity of delirium in the ICU. *Neurocrit Care*. 2005;2(2):150-8. doi: 10.1385/NCC:2:2:150
30. Gatz M, Driessen A, Eschweiler J, Tingart M, Migliorini F. Open versus minimally-invasive surgery for Achilles tendon rupture: a meta-analysis study. *Arch Orthop Trauma Surg*. 2021 Mar;141(3):383-401. doi: 10.1007/s00402-020-03437-z
31. Dinçer S. Eğitim Bilimlerinde Uygulamalı Meta-Analiz. Ankara, Turkey: Pagem Yayıncılık; 2021. ISBN 978-605-364-844-4
32. Oh ES, Li M, Fafowora TM, Inouye SK, Chen CH, Rosman LM, Lyketsos CG, Sieber FE, Puhan MA. Preoperative risk factors for postoperative delirium following hip fracture repair: a systematic review. *Int J Geriatr Psychiatry*. 2015 Sep;30(9):900-10. doi: 10.1002/gps.4233
33. Björkelund KB, Hommel A, Thorngren KG, Gustafson L, Larsson S, Lundberg D. Reducing delirium in elderly patients with hip fracture: a multi-factorial intervention study. *Acta Anaesthesiol Scand*. 2010 Jul;54(6):678-88. doi: 10.1111/j.1399-6576.2010.02232.x
34. Bilge EÜ, Kaya M, Şenel GÖ, Ünver S. The Incidence of Delirium at the Postoperative Intensive Care Unit in Adult Patients. *Turk J Anaesthesiol Reanim*. 2015 Aug;43(4):232-9. doi: 10.5152/TJAR.2015.93798
35. Nazemi AK, Gowd AK, Carmouche JJ, Kates SL, Albert TJ, Behrend CJ. Prevention and Management of Postoperative Delirium in Elderly Patients Following Elective Spinal Surgery. *Clin Spine Surg*. 2017;30(3): 112-119. doi: 10.1097/BSD.0000000000000467
36. Shah H, Shah R, Sanghani H, Lakhani N. Health related quality of life (HRQoL) and its associated surgical factors in diabetes foot ulcer patients. *J Clin Invest Surg*. 2020;5(2):83-90. doi: 10.25083/2559.5555/5.2/83.90
37. Yang Y, Zhao X, Gao L, Wang Y, Wang J. Incidence and associated factors of delirium after orthopedic surgery in elderly patients: a systematic review and meta-analysis. *Aging Clin Exp Res*. 2021 Jun;33(6): 1493-1506. doi: 10.1007/s40520-020-01674-1
38. Ayazoğlu TA, Tür H, Bolat C, Özkaynak İ, Candan MA. The prevalence and the risk factors for delirium in the elderly after cardiac surgery in intensive care unit. *J Exp Clin Med.* 2012;29:101-107. doi: 10.5835/jecm.omu.29.02.004 https://dergipark.org.tr/tr/download/article-file/190053
39. Inanc IH, Polat E, Coskun FY. One-year clinical follow-up and outcomes in patients after drug-eluting stent implantation for unprotected left main coronary stenosis: A single center study from Turkey. *J Clin Invest Surg*. 2020;5(1):43-50. doi: 10.25083/2559.5555/5.1/43.50
40. Freter SH, George J, Dunbar MJ, Morrison M, Macknight C, Rockwood K. Prediction of delirium in fractured neck of femur as part of routine preoperative nursing care. *Age Ageing.* 2005 Jul;34(4):387-8. doi: 10.1093/ageing/afi099
41. Güner P, Geenen O. Atlanması kolay bir bozukluk: Deliryum. *C.Ü. Hemşirelik Yüksekokulu Dergisi*. 2007;11(1):37-46. http://eskidergi.cumhuriyet.edu.tr/makale/1528.pdf