



Effect of personalized nursing based on quantitative evaluation strategies on remission of first-episode schizophrenia comparing to usual care: a systematic review and meta-analysis

Yan Tang, Linhua Yu, Xiaoyu Zhu, Jing Lyu, Huifen Lyu, Zhaoxia Yuan

Department of Psychiatry, Affiliated Mental Health Center and Hangzhou Seventh People's Hospital, Zhejiang University School of Medicine, Hangzhou, China

Contributions: (I) Conception and design: Y Tang; (II) Administrative support: Z Yuan; (III) Provision of study materials or patients: L Yu; (IV) Collection and assembly of data: X Zhu; (V) Data analysis and interpretation: J Lyu, H Lyu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Zhaoxia Yuan. Department of Psychiatry, Affiliated Mental Health Center and Hangzhou Seventh People's Hospital, Zhejiang University School of Medicine, 305 Tianmushan Road, Xihu District, Hangzhou 310013, China. Email: Yuanzx82@163.com.

Background: The drug control of symptoms is for now the main clinical treatment of schizophrenia, but patients' varying condition and poor compliance can also fluctuate the therapeutic effect. Personalized nursing with a quantitative evaluation strategy (PNQES) may help improve the compliance and symptoms, but there are controversies over the outcomes reported in each specific study; the meta-analysis method aims to resolve the controversies over studies, thus, we conducted this study to pooling the results of controlled clinical studies, and to systematically evaluate the effects of this nursing model.

Methods: The PubMed, Medline, Embase, China National Knowledge Infrastructure, and Wanfang databases were selected and searched for relevant articles for PNQES comparing to usual care. The inclusion criteria were established according to the Participants, Interventions, Comparisons, Outcomes, and Study (PICOS) framework. The Cochrane risk of bias 2.0 tool was used to evaluate the risk of bias of the included articles. The symptom scores, treatment compliance rate, quality of life, and social function indicators of the patients after nursing were quantitatively analyzed with effect sizes of mean difference (MD) or standard mean difference (SMD).

Results: The 11 included articles comprised a total of 1,251 patients with experimental group 625 and control group 626. Of all the 11 articles, only 1 had a "low" risk of bias, while the other articles had "some concern of risk;" none of the articles had a "high" risk of bias. The meta-analysis showed that patients who received PNQES had a significantly lower Positive and Negative Syndrome Scale (PANSS) total score after care than patients who received routine care [MD = -9.95, 95% confidence interval (CI): -14.35, -5.55; $P < 0.00001$]. Further, the treatment compliance rate of patients who received PNQES was significantly higher (odds ratio = 4.44, 95% CI: 2.17, 9.09; $P < 0.0001$), as was the quality of life (standard MD = 2.40, 95% CI: 1.46, 3.34; $P < 0.00001$). Further, the social function deficit score was significantly lower (MD = -2.25, 95% CI: -3.75, -0.76; $P = 0.003$). Subgroup and regression analyses showed that patient age, initial PANSS score, and the quantitative method of disease severity were not the sources of heterogeneity. Different intervention approaches applied may have been the source of heterogeneity.

Discussion: The application of PNQES is helpful for improving patients' symptoms and disease outcomes, treatment compliance, social function, and quality of life. It is suggested to be generalized in clinical application.

Keywords: Schizophrenia; quantitative evaluation; personalized care; nursing effect

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Introduction

Schizophrenia is a common serious psychiatric disease in clinical practice. During an attack of this disease, a patient's personal sensations, perceptions, emotions, and behaviors are abnormal. Some patients experience hallucinations and cannot distinguish between hallucinations and reality. Patients may be sluggish, withdraw, display excessive behavioral reactions, find it difficult to maintain normal social contacts, and have their quality of life seriously reduced, and both patients and their families are greatly affected (1,2).

According to statistics, about 23 million patients have been diagnosed with schizophrenia worldwide, and its lifetime prevalence is about 3.8–8.4% (3). In Asian populations, the disorder accounts for approximately 50% of all psychiatric disorders (4). The disease is characterized by repeated course migration, complex and variable symptoms, and high recurrence and disability rates (5). The drug control of symptoms is the main clinical treatment (5). Drug treatment has a good effect on positive symptoms, such as delusions and hallucinations, but its effect on negative symptoms, such as withdrawal and apathy, is limited. During the treatment, patients' social skills are poor, treatment compliance is poor, and self-management ability is poor too, all are the factors which could affect the drug treatment (6). Also, the detachment of patients' mental activity from reality and patients' tendency to violence are also major problems in nursing that causing nursing difficulties (6).

Quantitative evaluation and personalized nursing are two important areas in the field of nursing. Quantitative evaluation can digitize the patient's condition, rehabilitation status and other contents, while personalized nursing emphasizes the discovery of patients' different nursing needs and the formulation of differentiated schemes. The nursing model of the combination of the two has been gradually applied in different fields, and its application in psychiatry is also gradually being discussed (7). However, there are controversies in the reports of the effects of this care model among studies. In the controlled clinical studies implemented by Wang *et al.* (8) and Jiang *et al.* (9), the total Positive and Negative Syndrome Scale (PANSS) score of patients after personalized care under a quantitative evaluation strategy was significantly lower than usual care. However, in another study by Li *et al.* (10), there was no significant difference between the reduced value of PANSS score after nursing comparing to the usual

care. Thus, we conducted a combined meta-analysis to resolve the controversies and examine the significance of personalized nursing care with quantitative evaluation strategies in the treatment of schizophrenia. We present the following article in accordance with the PRISMA reporting checklist (available at <https://apm.amegroups.com/article/view/10.21037/apm-22-605/rc>).

Methods

Inclusion of studies

We determined inclusion criteria based on the Participants, Interventions, Comparisons, Outcomes, and Study (PICOS) framework (11). All the subjects in all the studies were patients with confirmed first-episode schizophrenia. The studies were all randomized controlled trials (RCTs), non-RCTs (e.g., cohort, case-control, cross-sectional, and heterogeneity studies) were excluded. The patients were randomly divided into the following 2 groups: (I) the experimental group; and (II) the control group. There was no significant difference in the baseline data between the 2 groups, and the same drug intervention and treatment were administered. However, the nursing methods administered to the 2 groups differed. The control group received routine nursing care, while the experimental group received personalized nursing with a quantitative evaluation strategy.

The nursing methods for the experimental group comprised the following 2 aspects: (I) a "quantitative evaluation strategy"; and (II) "personalized nursing". Under the quantitative evaluation strategy, a scale or method was used for enrollment, and the disease severity of each patient was scored, quantified, and graded according to the quantitative results. The PANSS is a common quantification method. Under the PANSS, patients with a score of >120 points are assessed as having severe symptoms, patients with a score of 80–120 points are assessed as having moderate symptoms, patients with a score of 60–80 points are assessed as having mild symptoms, and patients with a score of <60 points are assessed as having no obvious schizophrenic symptoms. Under the personalized nursing approach, different nursing methods are applied to patients depending on the severity grade (e.g., for severe patients, the nurse-patient ratio is increased, the frequency of the hospitalization patrol is increased, and an enhanced version of health education and rehabilitation training is adopted).

Literature search strategy

We used the mainstream medical databases of PubMed, Medline, Embase, China National Knowledge Infrastructure (CNKI), and Wanfang as the literature sources. The search period included articles published from the establishment of the databases to January 2022, and different search strategies were adopted for different databases. For example, for the PubMed database, the following search method was adopted:

- (I) Search quantitative evaluation strategy [Title/Abstract] OR schizophrenia [Title/Abstract]
- (II) Search rating [Title/Abstract] OR schizophrenia [Title/Abstract]
- (III) Search personalized nursing [Title/Abstract] OR schizophrenia [Title/Abstract]
- (IV) Search individualized nursing [Title/Abstract] OR schizophrenia [Title/Abstract]
- (V) Search #1 OR #2 OR #3 OR #4
- (VI) Search (schizophrenia [MeSH Terms]) OR nursing [Title/Abstract].

Literature selection and data extraction

Next, 2 researchers worked together to screen the articles according to the inclusion criteria. After finalizing the included articles, the full text of each article was obtained and read, and the required data were extracted, and recorded in a table. The extracted data included the (I) the baseline data of the included patients, including the gender composition ratio (%), age composition ratio (%), initial PANSS score (mean \pm variance), education level (%), residence, and family psychiatric history; and (II) the publication data, including the journal name, first author name, and region; and (III) the outcome data.

Outcome indicators

Due to the different outcome indicators reported in each article, we could not perform a meta-analysis for all of the outcome indicators; thus, only the following 4 most common indicators were analyzed: (I) PANSS score after nursing (the scores measured by the PANSS were divided into a positive symptom score, a negative symptom score, and a general psychotic symptom score, we only counted the total scores of the 3 aspects); (II) treatment compliance rate. (Patient compliance was assessed subjectively or objectively. Under the subjective method, the medical

staff subjectively assessed the patients. Under the objective method, the patients were assessed using a scale); (III) quality of life after nursing. Each study used different scales to assess patients' quality of life after care. Quality of life can be divided into material life, physical health, mental health, and social function, but we only analyzed patients' physical health scores; and (IV) social function after nursing {the social dysfunction scale [Social Disability Screening Schedule (SDSS)] score after nursing was used} (12).

Literature quality assessment and risk of bias

The Cochrane risk of bias 2.0 tool (13) was used to assess the risk of bias for the included studies. The risk of bias tool comprises 6 separate aspects, each judged by 3 levels of risk of bias, which are "low risk", "some concern of risk", and "high risk".

Statistical methods

The I^2 test and Q test were used to analyze the heterogeneity among the different studies. An I^2 value $<50\%$ or a P value ≥ 0.1 indicated no statistically significant heterogeneity; the PANSS score and SDSS score were continuous variables, and the mean difference (MD) and 95% confidence interval (CI) were used as the effect sizes; the odds ratio (OR) effect size was used for the dichotomous categorical variable of treatment compliance, and the 95% CI was used as the CI; due to the use of different scales of life treatment in each article, we used the standard mean difference (SMD) and 95% CI as effect sizes. If there was no statistically significant heterogeneity in the articles, the fixed-effects model was adopted. Conversely, if there was statistically significant heterogeneity in the articles, the random-effects model was adopted. The forest plot shows the merging process of the effect size; the heterogeneity source was investigated by a subgroup analysis and a meta-regression analysis. A sensitivity analysis was performed using the one-by-one exclusion method. Publication bias was quantitatively determined by Begg's test. P value <0.05 bilaterally could be considered statistically significant.

Results

Literature screening process and results

Initially, we retrieved 401 articles, but ultimately only 11 articles were included in the meta-analysis (8,9,14-22).

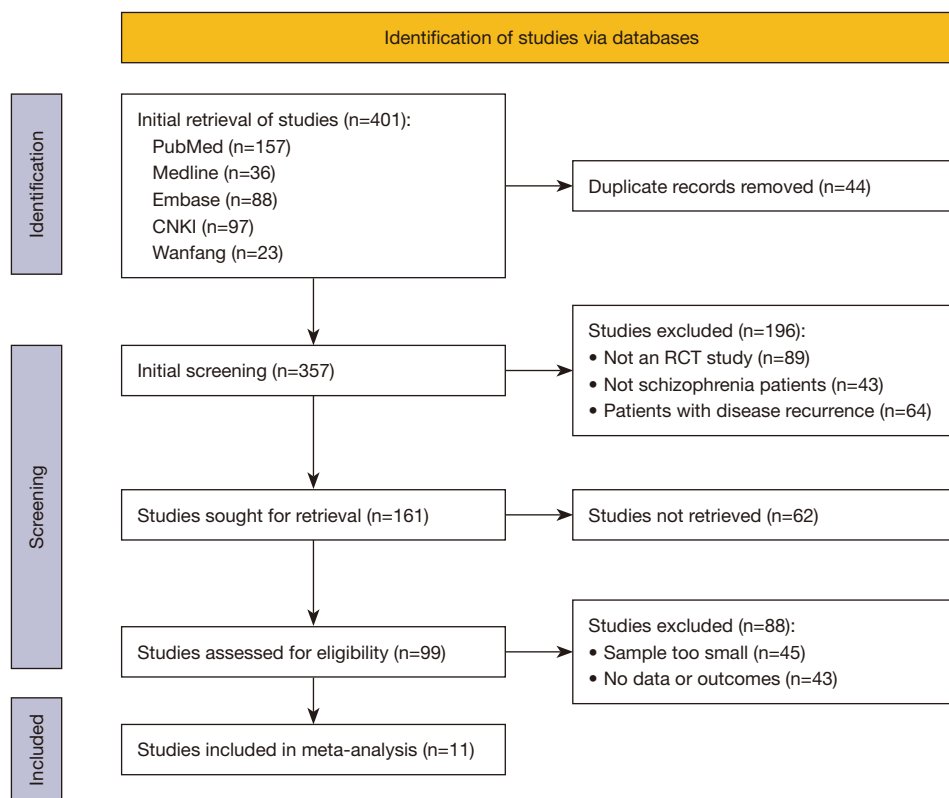


Figure 1 The selection flow chart. CNKI, China National Knowledge Infrastructure; RCT, randomized controlled trial.

Figure 1 shows the selection flow chart.

Basic characteristics of literatures

A total of 1,251 patients with schizophrenia were included in this study. All of the studies were RCTs, the subjects of 4 studies were children (aged <18 years) (8,14-16) and the subjects of the remaining 7 studies were adults. A total of 4 studies (16,17,20,21) included patients with an average baseline PANSS score <80, and the remaining 7 studies included patients with an average baseline PANSS scores ≥ 80 . A total of 6 studies (8,9,14-16,18) assessed patients' disease severity using the PANSS, and the remaining 5 studies were assessed by other means (see Table 1).

Quality assessment of literature

The overall quality of the 11 studies included in this meta-analysis was good. In relation to the risk of bias, 1 article (16) had a "low" risk of bias, and the other articles had "some concern of risk"; none of the articles had a "high" risk of bias (see Figures 2,3).

Meta-analysis results

PANSS total score after nursing

All of the 11 articles compared the average PANSS scores of patients before and after nursing. There was no statistically significant difference in the PANSS scores between the 2 groups before nursing in the reports of all the 11 studies. As the meta-analysis revealed that there was statistical heterogeneity between the articles comparing the PANSS scores after nursing ($I^2=99\%$, $P<0.00001$), the random-effects model was used. The results of the pooled analysis showed that patients who received personalized nursing with a quantitative evaluation strategy had a significantly lower total PANSS score after nursing than patients who received routine nursing (MD = -9.95, 95% CI: -14.35, -5.55; $P<0.00001$; see Figure 4).

Treatment compliance rate after nursing

Only 4 articles (8,9,14,15) examined the treatment compliance rate of patients. As there was no statistical heterogeneity among the articles ($I^2=0\%$, $P=0.89$), the fixed-effects model was used to pool the data of the studies. Patients who

Table 1 Basic characteristics of the included studies

First author, year	Type of study	Control group		Experimental group		Population (E/C)	Baseline PANSS total score ($\bar{x}\pm SD$)	Method for quantifying disease severity	Outcome indicators
		M/F	Age (y, $\bar{x}\pm SD$)	M/F	Age (y, $\bar{x}\pm SD$)				
Wang <i>et al.</i> 2018 (8)	RCT	27/13	10.29±1.42	24/16	10.84±1.24	40/40	94.68±8.12	PANSS	(a)(b)(c)
Jiang <i>et al.</i> 2020 (9)	RCT	30/25	44.4±4.0	29/26	43.2±6.2	55/55	94.02±5.12	PANSS	(a)(b)(d)
Ye <i>et al.</i> 2021 (14)	RCT	19/21	15.85±1.68	18/22	15.76±1.70	40/40	93.25±5.08	PANSS	(a)(b)(c)
Shao <i>et al.</i> 2021 (15)	RCT	17/13	13.88±1.92	16/14	13.92±1.80	30/30	92.14±3.27	PANSS	(a)(b)(c)
Qin <i>et al.</i> 2021 (16)	RCT	63/37	10.9±1.8	60/40	9.1±1.1	100/100	77.25±3.14	PANSS	(a)(c)(d)(e)
Chen <i>et al.</i> 2021 (17)	RCT	16/32	55.67±5.47	18/30	56.59±5.53	48/48	66.89±6.24	CGI-SI	(a)(c)(d)(e)(f)(g)
Shimada <i>et al.</i> 2018 (18)	RCT	33/35	41.39±11.04	34/34	43.34±9.97	68/68	108.53±20.33	PANSS	(a)
Gu <i>et al.</i> 2014 (19)	RCT	15/18	23.39±10.34	14/18	24.03±8.24	32/33	82.82±9.54	PSP	(a)
He <i>et al.</i> 2017 (20)	RCT	34/28	39.62±7.68	33/29	40.16±7.63	62/62	58.69±8.66	HAD	(a)(c)(f)
Xu <i>et al.</i> 2016 (21)	RCT	50/50	32.66±10.58	50/50	32.85±11.16	100/100	59.04±7.33	BPRS	(a)
Chen <i>et al.</i> 2019 (22)	RCT	25/25	34.75±9.82	25/25	35.82±10.93	50/50	93.42±3.66	BPRS	(a)

(a) PANSS total score; (b) treatment compliance rate; (c) quality of life; (d) SDSS score; (e) the SSMIS score; (f) the MRSS score; (g) recurrence rate. M/F, male/female; E/C, experimental/control; PANSS, Positive and Negative Syndrome Scale; CGI-SI, Clinical Global Impression-Severity of illness; PSP, Personal and Social Performance Scale; HAD, Hospital Anxiety and Depression Scale; BPRS, brief psychiatric rating scale; SDSS, Social Disability Screening Schedule; SSMIS, schizophrenia self-management instrument scale; MRSS, morning side rehabilitation status scale.

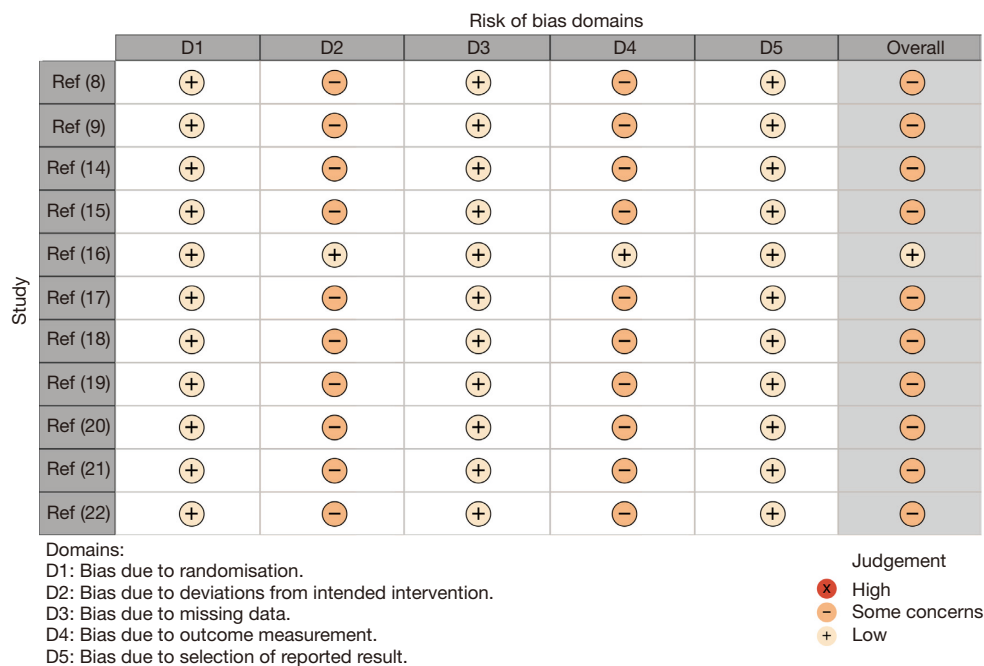


Figure 2 Detailed plot of literature bias analysis.



Figure 3 Summary plot of literature bias analysis.

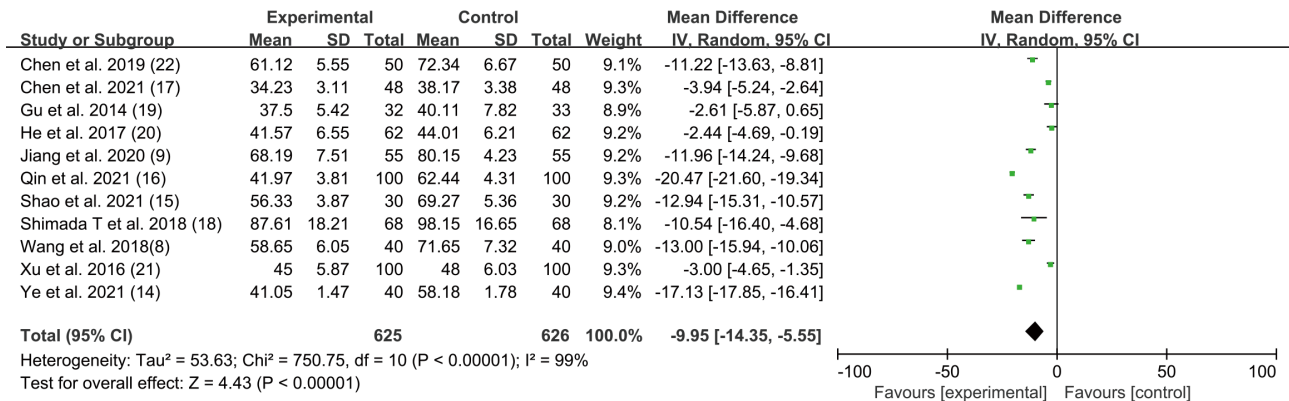


Figure 4 Comparison of PANSS total scores after nursing between the 2 groups. PANSS, Positive and Negative Syndrome Scale.

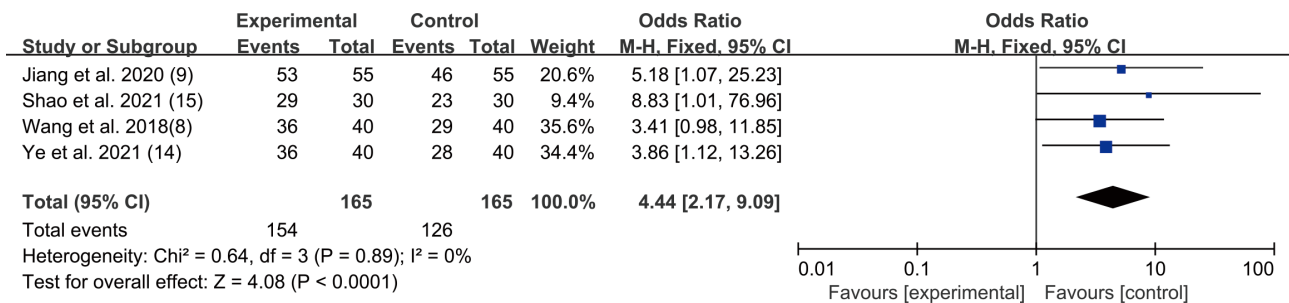


Figure 5 Comparison of treatment compliance rates after nursing between the 2 groups.

received personalized nursing with a quantitative evaluation strategy had a significantly higher treatment compliance rate than patients who received routine nursing care (OR =4.44, 95% CI: 2.17, 9.09, P<0.0001; see Figure 5).

Quality of life after nursing

Only 6 articles (8,14-17,20) examined quality of

life indicators after nursing. As there was statistical heterogeneity among the articles (I²=95%, P<0.00001), the random-effects model was used to pool the data. Patients who received personalized nursing with a quantitative evaluation strategy had a significantly higher quality of life after nursing than patients who received routine nursing (SMD =2.40, 95% CI: 1.46, 3.34, P<0.00001; see Figure 6).

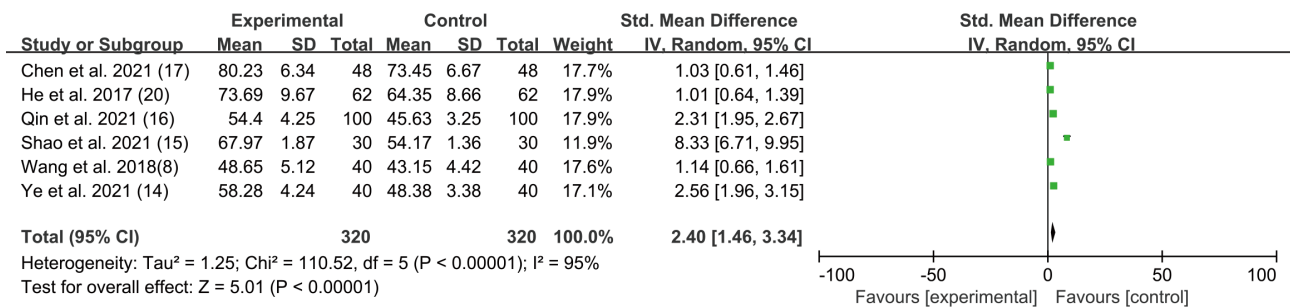


Figure 6 Comparison of quality of life after nursing between the 2 groups.

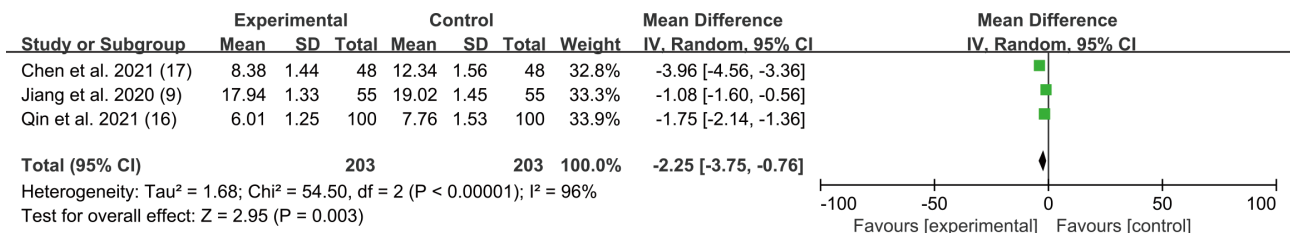


Figure 7 Comparison of SDSS scores after nursing between the 2 groups. SDSS, Social Disability Screening Schedule.

SDSS score after nursing

Only 3 articles (9,16,17) reported SDSS scores. As there was statistical heterogeneity between the articles ($I^2=96\%$, $P<0.00001$), the random-effects model was used to pool the data. The patients who received personalized nursing with a quantitative evaluation strategy had significantly lower SDSS scores after nursing than those who received routine nursing (MD = -2.25, 95% CI: -3.75, -0.76; $P=0.003$; see Figure 7).

Subgroup analysis and regression analysis

Grouping by age

The 11 articles were divided into “children” and “adult” groups according to whether the study subjects were adults or children. For the subgroup analysis of the pooled effect size of PANSS total scores after nursing, there was still heterogeneity among the 2 subgroups, indicating that age was not the source of heterogeneity (see Figure 8).

Grouping by initial PANSS scores

The 11 articles were divided into “ ≥ 80 ” and “ < 80 ” groups according to the PANSS baseline score at enrollment. For the subgroup analysis of the PANSS total scores after nursing, there was still heterogeneity in the 2 subgroups, indicating that the initial PANSS of patients was not the source of heterogeneity (see Figure 9).

Grouping by quantification of disease severity

The 11 articles were divided into “PANSS assessment” and “non-PANSS assessment” groups according to the quantitative method used to determine disease severity at enrollment. For the subgroup analysis of the pooled effect size of the PANSS total scores after nursing, there was still heterogeneity in the 2 subgroups, indicating that the use of the PANSS to assess the disease severity of patients was not the source of heterogeneity (see Figure 10).

Quantitative regression analysis

A meta-regression was used to replace the quantitative methods of patient age, initial PANSS score, and disease severity into the regression equation. The P values of the 3 factors were all >0.05 , indicating that none of these 3 factors was a statistically significant factor affecting the results of the meta-analysis (see Table 2). The bubble plots with age and initial PANSS score in abscissa are shown in Figures 11,12.

Sensitivity analyses

Our sensitivity analysis of the PANSS total scores after care in both groups (see Figure 13) revealed that the results of studies (16,21) fell outside the upper and lower limits of 95% confidential interval, and that this may have been the source of heterogeneity.

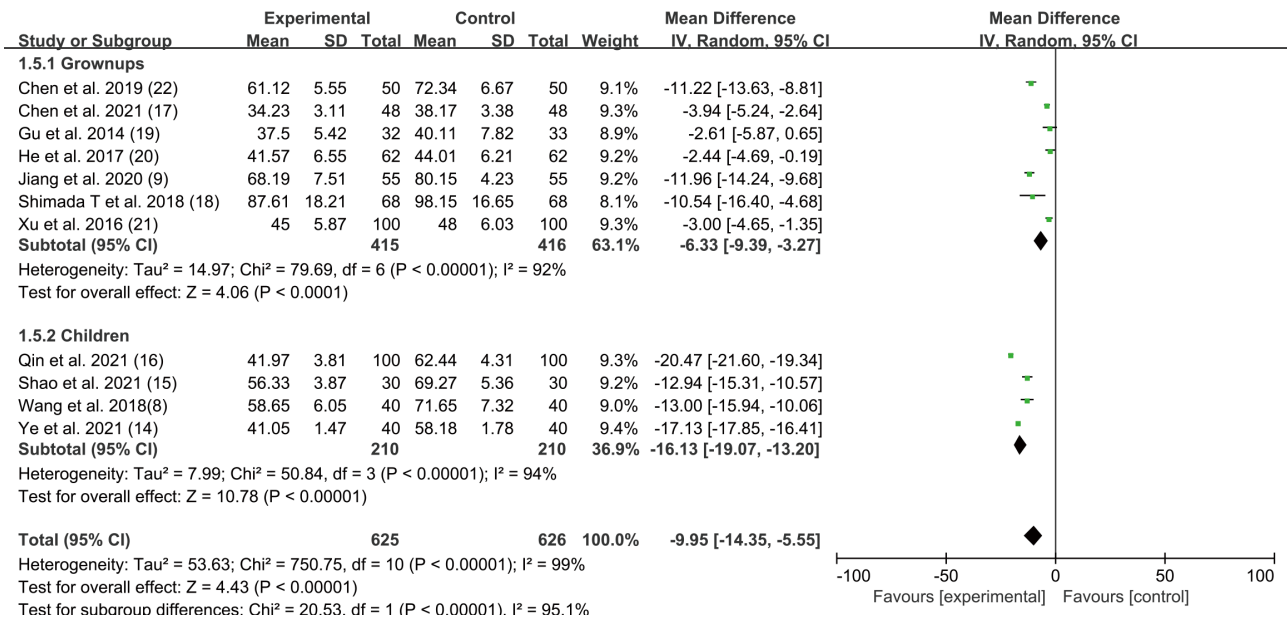


Figure 8 Analysis of PANSS total scores after nursing in 2 groups: grouped by age. PANSS, Positive and Negative Syndrome Scale.

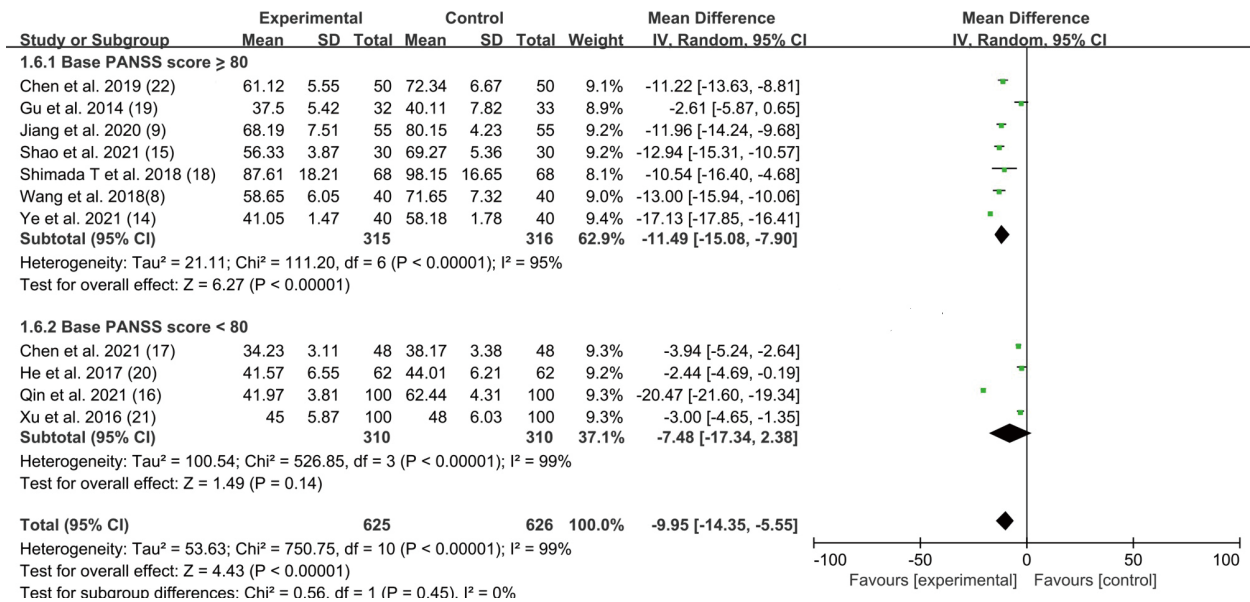


Figure 9 Analysis of PANSS total scores after nursing in 2 groups: grouped by the initial PANSS score. PANSS, Positive and Negative Syndrome Scale.

Analysis of publication bias

For the Begg’s test of the PANSS total scores after nursing for the 2 groups, we found that $P > |t| = 0.042$, suggesting that there may be a small degree of publication bias (see Figure 14).

Discussion

Schizophrenia is a mental illness induced by a combination of genetics, changes in the cerebral nervous system, changes in human hormones, and the acquired environment, and its pathogenesis and triggers are still not very clear (23-25).

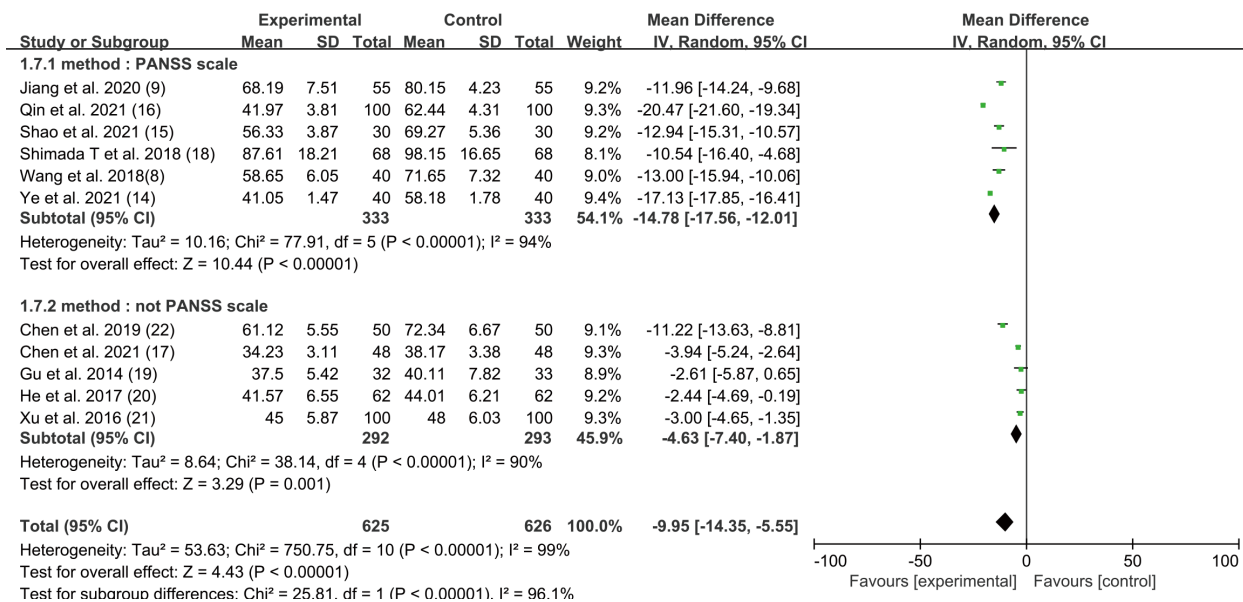


Figure 10 Analysis of PANSS total scores after nursing in 2 groups: grouped by the disease severity quantification method. PANSS, Positive and Negative Syndrome Scale.

Table 2 Meta-regression analysis results

Covariate	β	Std. Err.	t	P> t	95% CI
PANSS	0.0235068	0.0740221	0.32	0.760	-0.1515275 to 0.1985412
Age	0.0599563	0.0662756	0.90	0.396	-0.0967606 to 0.2166731
Scale	-2.479465	2.572058	-0.96	0.367	-8.561415 to 03.602485
_Cons	-4.790085	5.714544	-0.84	0.430	-18.30284 to 8.722665

PANSS, Positive and Negative Syndrome Scale.

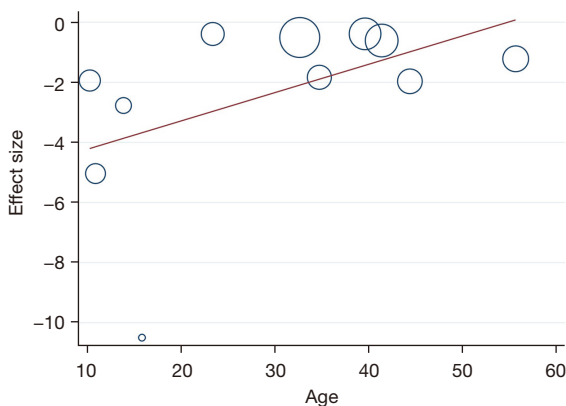


Figure 11 Meta-regression analysis: age.

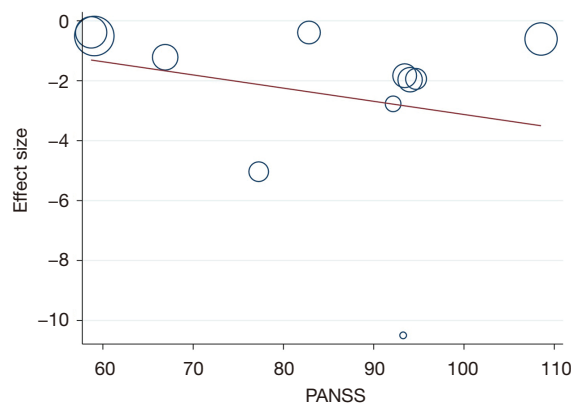


Figure 12 Meta-regression analysis: initial PANSS score. PANSS, Positive and Negative Syndrome Scale.

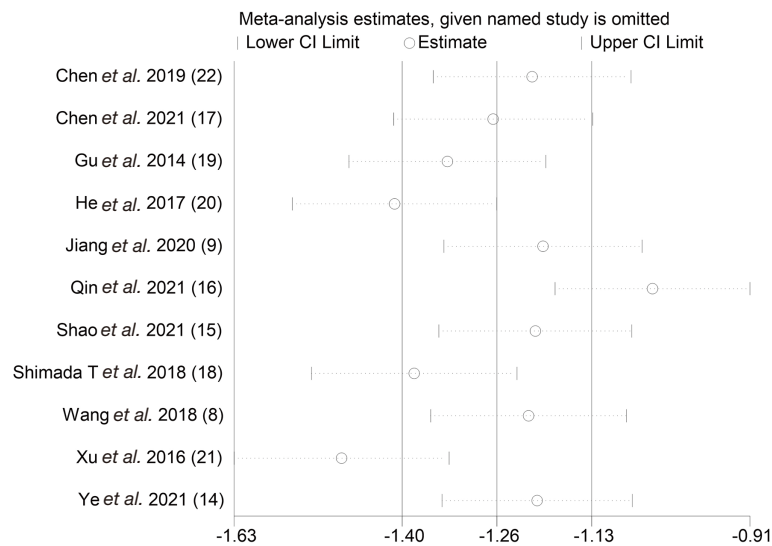


Figure 13 Sensitivity analysis of PANSS total scores after nursing in the 2 groups. PANSS, Positive and Negative Syndrome Scale.

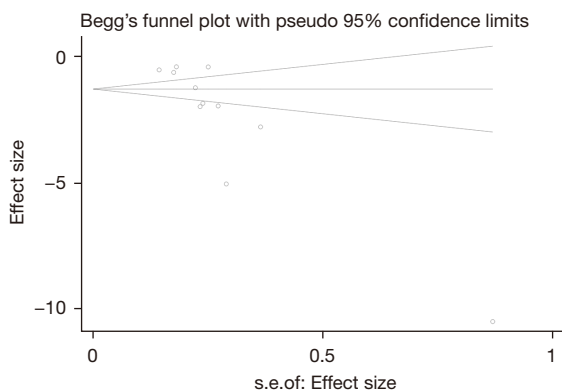


Figure 14 Begg's test analysis of PANSS total scores after nursing in the 2 groups. PANSS, Positive and Negative Syndrome Scale.

Patients with brain dysfunction, resulting in cognitive, emotional, sensory, volitional, and other mental activities, experience impairments, and the symptoms of schizophrenia are complex and variable (26,27). Patients often do not cooperate with treatment, which creates obstacles in the prognosis and outcomes of the disease (26,27). Thus, effective nursing interventions are needed to ensure smooth treatment.

Traditional nursing applies the same intervention measures to all patients, fails to consider the different disease states and nursing needs of different patients, and is very limited in terms of its clinical treatment efficacy. Conversely, personalized nursing with a quantitative

evaluation of the initial severity of the disease with scientific scales, implements differentiated resource allocations and nursing intensity for patients with different symptoms and severity levels, so as to meet the needs of different patients, and improve nursing efficiency (28-31).

In this study, 11 RCT studies were included. All the articles examined the effects of routine nursing and personalized nursing with a quantitative evaluation strategy on the PANSS scores of patients. The pooled effect size showed that the PANSS scores after nursing in the experimental group were lower than those in the control group (MD = -9.95), and the treatment compliance was higher in the experimental group than the control group (OR = 4.44). PANSS is an internationally accepted schizophrenia symptom severity assessment table, which is divided into 3 domains (positive symptoms, negative symptoms, and general psychiatric symptoms), and can be used to diagnose schizophrenia. Clinically, a PANSS score <60 points is often used as the cut-off line for disease diagnosis, while a PANSS score >80 points indicates a moderate grade, and a score PANSS >120 points indicates a severe grade (32,33). Thus, the reduction in PANSS scores shows the effectiveness of the personalized nursing model with a quantification-based evaluation strategy.

Quantitative evaluations and personalized care are 2 frontier branches in the field of care. A quantitative evaluation assesses and quantifies a patient's condition, rehabilitation status with perceivable indicators and presents with digital data (34). Personalized care emphasizes

respecting the individual differences of each patient and discovering the different needs of each patient through surveys to develop differentiated care plans and meet diversified care needs. The 2 have been combined and applied in the nursing process of patients with first-episode schizophrenia to assess symptoms, understand the disease status of each patient, and implement different care plans for each patient (35).

In study (8), a stratified nursing approach was carried out for the experimental group whereby mild patients were allocated resources with a nurse-patients ratio of 1:3 and room tours every 15–30 min, moderate patients were allocated resources with a nurse-patients ratio of 1:2 and room tours every 15 min, and severe patients were placed in a special ward with a configuration of nurse-patients ratio 1:1. Based on the characteristics of age and education level, patients can be provided with different levels of health education and rehabilitation nursing to cultivate their social skills, stabilize their psychological cognition, strengthen their self-management, prepare them for the better prognosis outcomes, and help them return to society. In the implementation process of nursing interventions, the subjective initiative of patients is fully mobilized, and passive treatment is transferred to active treatment to cultivate patients' self-management abilities and minimize their psychiatric symptoms. A major feature of schizophrenia is the poor compliance (36,37). The use of both a quantitative evaluation and personalized nursing focuses the intervention on the characteristics of patients at different disease stages to effectively meet their nursing needs and improve their treatment compliance (29).

In this study, data on the quality of life and social function of the patients were also combined and analyzed. The results showed that the quality of life of the patients in the experimental group was better than that of the control group, while the social function defect score of the experimental group was lower than that of the control group. Our findings indicate that the nursing model combining quantitative evaluation with personalized nursing was helpful in improving the social function defect, quality of life, and symptoms of the patients.

The results of this study affirm the effectiveness of personalized care models with quantitative evaluation strategies; however, we also note that there was a large heterogeneity among the articles in the process of the pooling analyses for the post-care PANSS measures. We conducted subgroup and meta-regression analyses according to different ages, the initial PANSS total score,

and the quantitative method of the study subjects, and found that age, the initial PANSS total score, and the quantitative method were not factors affecting the results of the meta-analysis. We performed a case-by-case sensitivity analysis and found that studies (16,21) may causing heterogeneity, presumably because of the participants were all in their remission and from communities. We also note that while all the studies adopted a care model combining quantitative evaluation with personalized care, the details of the interventions varied, which may be a source of heterogeneity. In addition, quantitative evaluations and personalized care lack the support of nursing theory and guidelines, studies vary in the content and definition of personalized care, and there is a lack of uniform standards, all of which limit the application of this care model. Begg's test quantifying the publication bias in the combined analysis revealed that the study had a small risk of bias; thus, the application of a personalized care model with a quantitative evaluation strategy to care for patients with schizophrenia requires further in-depth research.

Conclusions

The condition of schizophrenia is complex and changeable, and the treatment compliance of patients is low. The use of a personalized nursing model with a quantitative evaluation strategy is helpful in improving patients' symptoms, disease outcomes, treatment compliance, social function, and quality of life.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at <https://apm.amegroups.com/article/view/10.21037/apm-22-605/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://apm.amegroups.com/article/view/10.21037/apm-22-605/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

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