Systematic Review and Meta-Analysis

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Efficacy and safety of methylprednisolone against acute respiratory distress syndrome

A systematic review and meta-analysis

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Abstract

Background: Acute respiratory distress syndrome (ARDS) is caused by an inflammatory injury to the lung. Dysregulated inflammation is the cardinal feature of ARDS. Methylprednisolone is an option for treating ARDS. However, the benefits and adverse effects of methylprednisolone have not been well assessed in patients with ARDS. This study aimed to evaluate the efficacy and safety of methylprednisolone against ARDS.

Material and methods: The electronic database of Embase, PubMed, the Cochrane Library, CNKI, and Wanfang were searched, and randomized controlled trials (RCTs) reporting the efficacy and safety of methylprednisolone for ARDS were included. Revman 5.3 and Stata 15.0 were used to conduct the analysis. The fixed-effects model was used to calculate summary odds ratios (ORs) and 95% confidence interval (CIs).

Results: Ten RCTs studies involving 692 patients with ARDS. The summary results demonstrated that, compared with placebo, methylprednisolone had a statistically significant effect on mortality (OR = 0.64; 95% CI: 0.43–0.95, $I^2 = 42\%$); the time of mechanical ventilation (MD) = –2.70, 95% CI: –3.31 to –2.10; $I^2 = 0\%$) in patients with ARDS, but it was not associated with increased rates of adverse events (OR = 0.80; 95% CI: 0.34–1.86; $I^2 = 58\%$).

Conclusions: This systematic review and meta-analysis demonstrated that Methylprednisolone is safe against ARDS. It may reduce mortality and shorten the time of mechanical ventilation. However, well-designed and large-sample studies were required to fully characterize the efficacy and safety of methylprednisolone against ARDS.

Abbreviations: ARDS = Acute respiratory distress syndrome, CIs = confidence interval, MD = mean differences, ORs = odds ratios, PRISMA = the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs = randomized controlled trials.

Keywords: adverse events, ARDS, mechanical ventilation, meta-analysis, methylprednisolone, mortality

1. Introduction

Acute respiratory distress syndrome (ARDS) is caused by an inflammatory injury to the lung. It is characterized by acute hypoxemic respiratory failure clinically.[1] The mortality rate in ARDS remains high, despite advances in critical care medicine over the past decades. Dysregulated inflammation is the cardinal feature of ARDS.[2]

Methylprednisolone has been considered a potentially beneficial therapy. It is an end-effector of the hypothalamic-pituitary-adrenal axis, and the most important physiologic inhibitors of inflammation.[3] It can affect hundreds of genes involved in stress-related homeostasis.[4] Methylprednisolone exerts its effects by activating cytoplasmic heat shock protein–complexed glucocorticoid receptors at the cellular level. Furthermore, it can prevent DNA binding and subsequent transcriptional activity by interacting with activated nuclear factor-kB.[4] Still, methylprednisolone can have adverse effects that might overshadow its therapeutic effects, including psychic adverse events, iatrogenic Cushing syndrome, infections, and osteoporosis.[5–7]

However, previous randomized trials failed to provide convincing evidence to prove the efficacy of corticosteroids in decreasing the mortality of ARDS. Meduri et al[8] demonstrated that methylprednisolone reduced mortality and was associated with an improvement in lung injury. However, Steinberg et al[9]

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showed that the use of methylprednisolone against ARDS might increase the risk of death.

The use of methylprednisolone in treating ARDS has gained increasing attention. A few studies summarized the efficacy and safety of methylprednisolone against ARDS. Hence, this systematic review and meta-analysis was performed to evaluate the efficacy and safety of methylprednisolone against ARDS.

2. Materials and methods

2.1. Search strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.[10] A keyword search was performed in Embase, PubMed, the Cochrane Library, CNKI, and Wanfang databases using the following terms: "methylprednisolone" AND ("acute lung injury" OR "ARDS" OR "acute respiratory distress syndrome") from inception to February 1, 2020. No language restrictions were applied. Also, the bibliographies of retrieved studies and recent review articles were screened to identify additional trials.

2.2. Inclusion and exclusion criteria

The following selection criteria were used to perform this meta-analysis according to the PICOS principles: participants (P)—patients with ARDS; intervention (I)—methylprednisolone; comparison (C)—other interventions; outcomes (O)—efficacy and safety; study design (S)—randomized controlled trials (RCTs). Studies were excluded if they were published as reviews, editorials, letters, case reports, cell and animal studies, or expert opinions. Two authors independently and systematically screened the literature by titles and abstracts, and then read the full texts to identify their eligibility. If >1 study were found in the same dataset, only the one with the largest sample size was included. Any disagreement in the literature search was resolved by the involvement of a third researcher.

Data were extracted and summarized into simple standard forms including the following contents: study, year, number of samples, age, dose of methylprednisolone, and follow-up.

2.3. Risk-of-bias assessment

The risk-of-bias assessment was evaluated according to the Cochrane Handbook for Systematic Reviews containing the selective outcome, allocation concealment, blinding, incomplete outcome data, random generation, and other biases. The quality of included studies was assessed by 2 reviewers.[11] Any disagreement in data extraction was resolved by the involvement of a third researcher.

2.4. Data synthesis and statistical analysis

The continuous variable data were expressed as mean differences (MD) with 95% confidence intervals (CIs). Odds ratios (ORs) and 95% CI were calculated to combine the categorical variable data in this meta-analysis.[9,10] The missing standard deviations, such as *P* values or 95% CI, were derived and estimated if needed. Among combined study results, Cochran Q test and degree of inconsistency (I^2) were used to assess heterogeneity. A fixed-effects model was used if I^2 was <50%. Otherwise, data were pooled using the random-effects model. The results of this study were statistically analyzed using Review Manager version 5.3 and the Stata Statistical Software Package, Version 15.0 (StataCorp LP, College Station, TX). Publication bias was estimated using the funnel plot. A P value <0.05 indicated statistical significance.

3. Results

3.1. Search results

A total of 495 studies were screened, and 256 potential ones were selected after removing duplicates in a combined search of Embase, PubMed, the Cochrane Library, CNKI, and Wanfang databases from inception until February 1, 2020. Of these, 150 were excluded, and a full-text review of the remaining 106 studies was performed. Furthermore, 96 additional studies were excluded according to the inclusion and exclusion criteria. Ten studies, including 692 patients, published from 1987 to 2019, were included in quantitative combination in this meta-analysis.[1,8,9,12–19] A flow diagram of the selection process is shown in Figure 1.

3.2. Characteristics of studies

In this study, the sample size ranged from 8 to 229, and the time of follow-up was from 1 week to 30 months. The baseline characteristics of these 10 studies in the meta-analysis are summarized in Table 1. Five studies used an adequate method of random sequence generation, including a computer-generated program in 2 studies and a randomized code in 3 studies. The adequate allocation concealment and blinding were implemented in 4 studies. The quality of the included studies is summarized in Figure 2A and Figure 2B.

3.3. Efficacy of methylprednisolone for ARDS

Regarding mortality, 6 studies ($N=485$) were combined, which used the number of deaths as an outcome measure, revealing a significant difference between methylprednisolone and placebo (OR = 0.64; 95% CI: 0.43–0.95; $I^2=42\%$) (Fig. 3).

Regarding the rates of adverse events, 5 studies ($N=484$) were combined, revealing no significant difference between methylprednisolone and placebo (OR = 0.80; 95% CI: 0.34–1.86); $I^2=58\%$) (Fig. 4). Meta-regression analyses revealed that the number of samples ($B=0.007$; $Z=1.77$; $P=.175$), publication year ($B=-0.16$; $Z=-0.53$; $P=.633$), mean age of patients in the intervention group ($B=0.067$; $Z=0.51$; $P=.642$), and mean age of patients in the control group ($B=-0.012$; $Z=-0.09$; $P=.934$) had no moderating effects on the rate of adverse events. The sensitivity analysis found that the study of Steinberg was the source of heterogeneity when each study was removed sequentially.

Regarding the time of mechanical ventilation, 4 trials ($N=231$) were included in the meta-analysis. A significant difference was found between methylprednisolone and placebo (MD = –2.70; 95% CI: –3.31 to –2.10; $I^2=0\%$) (Fig. 5).

3.4. Publication bias

Funnel plots (Fig. 6) and Egger tests did not show publication bias across studies with data on adverse events ($t=-1.93$; 95% CI:

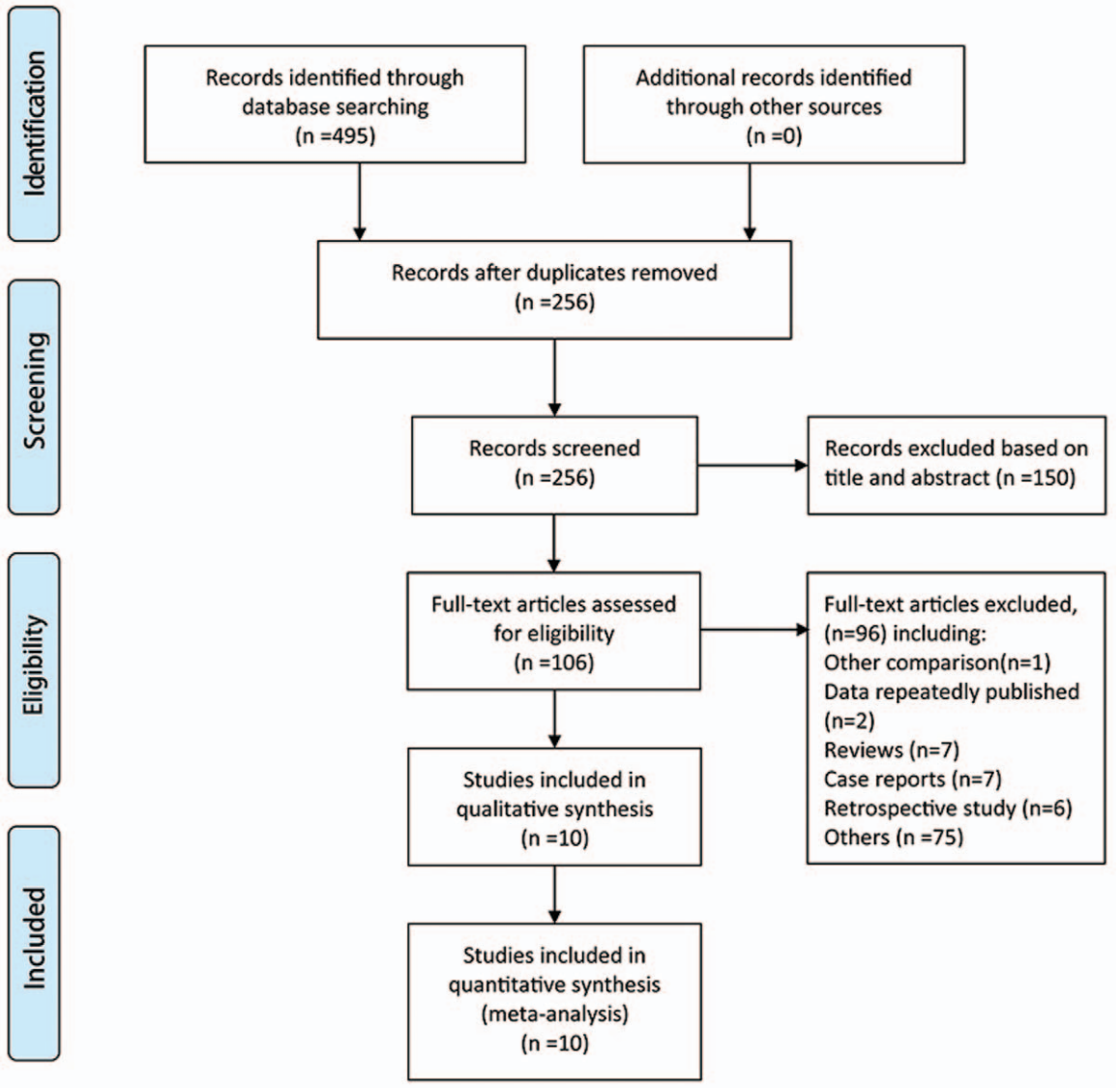

Figure 1. Flow chart of literature screening and selection process.

Table 1

Baseline characteristics of studies.

Study, year	Sampe size	Country	Age (mean, SD)		Dose of MET	Follow-up
			MET	Placebo		
Bernard et al, 1987[1]	99	America	55 (2)	56 (2)	NM	30 mo
Rezk et al, 2013[17]	27	Egypt	42.7 (14.0)	50.4 (14.0)	0.125–0.5 mg/(kg d)	1 mo
Steinberg et al, 2006[19]	180	America	49 (19)	49.2 (16.5)	0.5–2 mg/(kg d)	NM
Meduri et al, 2007[18]	91	America	50.1 (15.3)	53.2 (15.3)	0.125–0.5 mg/(kg d)	1 mo
Meduri et al, 1998[8]	24	America	47 (3.9)	51 (6.6)	0.125–2 mg/(kg d)	32 days
Li et al, 2016[12]	49	China	52.1 (10.6)	53.3 (9.8)	80 mg/d	NM
Wu et al, 2019[13]	90	China	51.2 (4.8)	51.6 (4.2)	120 mg/d	NM
Han et al, 2019[14]	50	China	47 (10)	49 (9)	1–2 mg/(kg d)	NM
Dai et al, 2011[15]	42	China	40.9 (4.9)	40.5 (5.2)	120 mg/d	NM
Huang et al, 2017[16]	40	China	NM	NM	80 mg/d	7 days

MET = methylprednisolone, NM = not mentioned.

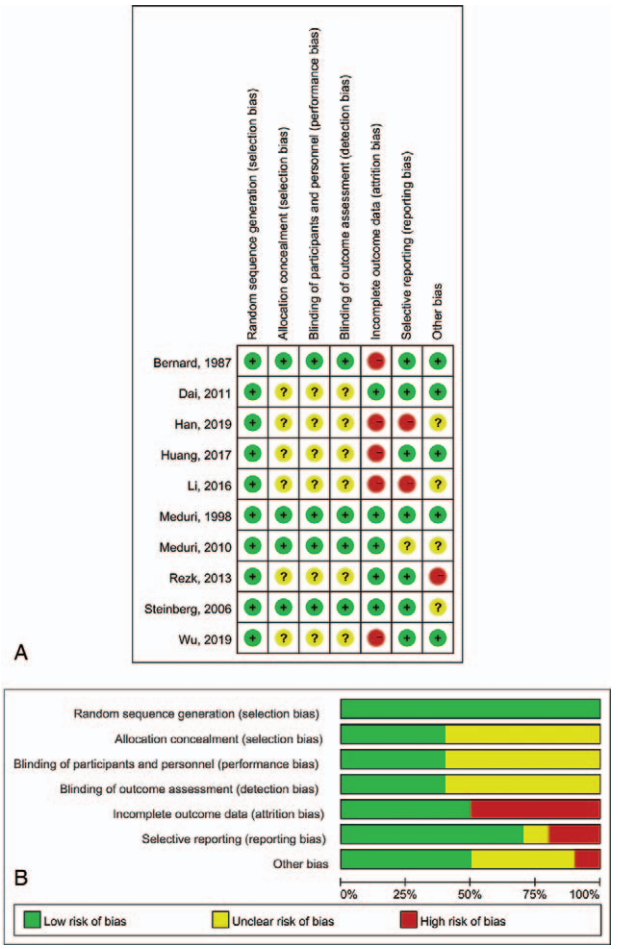

Figure 2. Quality assessment of included studies: (A) risk-of-bias graph; (B) risk-of-bias summary.

−6.09 to 1.49; $P=.149$) (Supplementary Figure 1, http://links.lww.com/MD/G1) and time of mechanical ventilation ($t=-1.73$; 95% CI: −18.5 to 7.91; $P=.226$) (Supplementary Figure 2, http://links.lww.com/MD/G1). However, they showed publication bias across studies with data on mortality ($t=-4.04$; 95% CI: −4.04 to −4.48; $P=.027$) (Supplementary Figure 3, http://links.lww.com/MD/G1).

4. Discussion

This systematic review and meta-analysis identified 10 RCTs investigating the effect of methylprednisolone on ARDS. The analysis found that treatment with methylprednisolone was associated with a significant reduction in mortality rate and time of mechanical ventilation, and methylprednisolone treatment was not associated with the rates of adverse events.

Several recent large multicenter RCTs assessed the effects of methylprednisolone in patients with ARDS. These trials assessed the effects of corticosteroids on mortality, time of mechanical ventilation, and rates of adverse events. Meduri et al's study[1,8,9,12–18] concluded that methylprednisolone-induced downregulation of systemic inflammation was associated with a significant improvement in pulmonary and extrapulmonary organ dysfunction and reduction in the duration of mechanical ventilation and length of stay in the intensive care unit. Rezk et al[17] demonstrated that methylprednisolone, when used on the first 2 days in patients with ARDS, improved the lung injury score and decreased systemic inflammation, earlier extubation from mechanical ventilation, and incidence of hospital-acquired infection. However, the study by Steinberg et al[18] did not support the routine use of methylprednisolone against persistent ARDS despite the improvement in cardiopulmonary physiology. In addition, starting methylprednisolone therapy more than 2 weeks after the onset of ARDS might increase the risk of death. These studies and other trials were summarized, demonstrating that methylprednisolone could reduce the mortality rate and shorten the time of mechanical ventilation. Methylprednisolone may affect muscle function, but its effects in critically ill patients are not well understood. Recent studies showed that patients receiving assisted ventilation showed a strong association between muscle weakness and methylprednisolone.[8,20] Methylprednisolone increased the severity but not the incidence of neuromyopathy.[21,22] The present study found that methylprednisolone treatment was not associated with the rates of adverse events compared with placebo. The safety of methylprednisolone for ARDS should be further explored.

This analysis still had some limitations. First, it showed a significant risk of reporting bias and selection and the risk-of-bias evaluation, although all included studies were RCTs. Second, it lacked evidence regarding safety during a long follow-up. Third, the specific side effects of methylprednisolone could not be analyzed because of inconsistent and nonuniform reporting among the included studies, and only the adverse events as a whole could be analyzed. Fourth, there were wide differences in

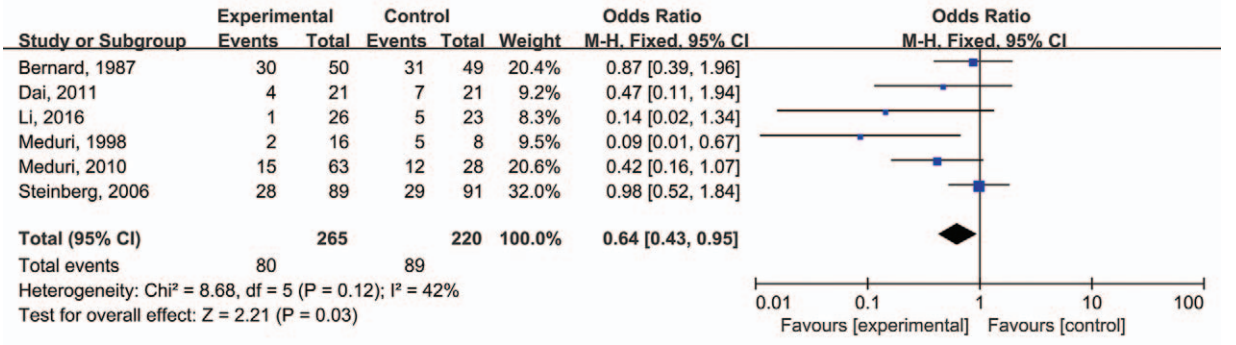

Figure 3. A meta-analysis of photodynamic therapy for efficacy.

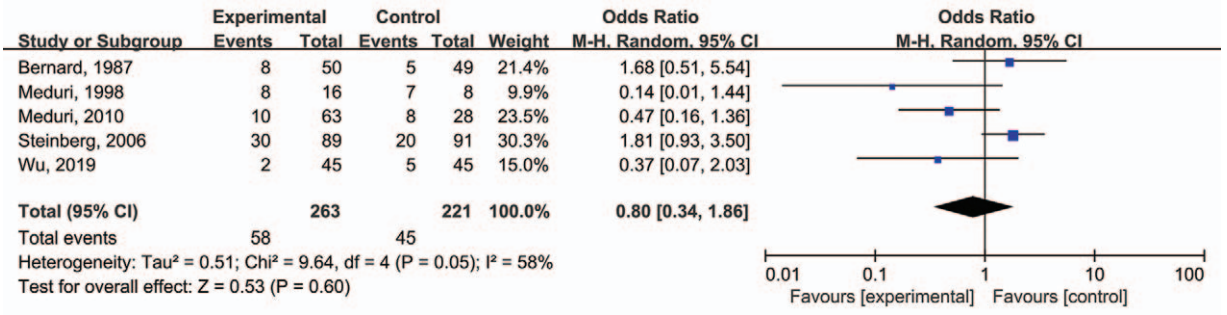

Figure 4. A meta-analysis of photodynamic therapy for recurrence.

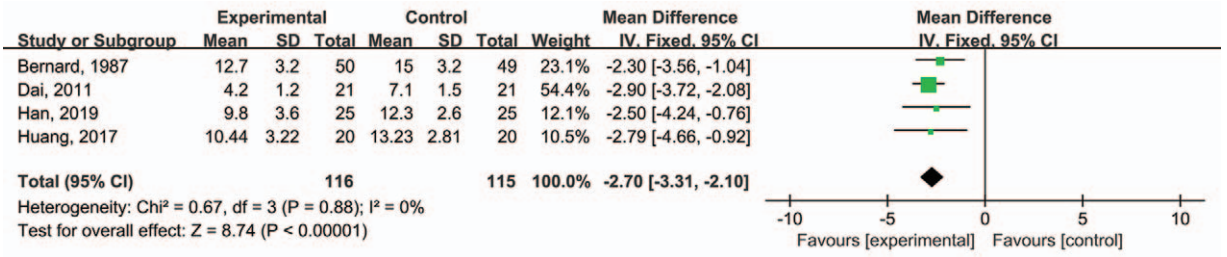

Figure 5. A meta-analysis of photodynamic for time of mechanical ventilation.

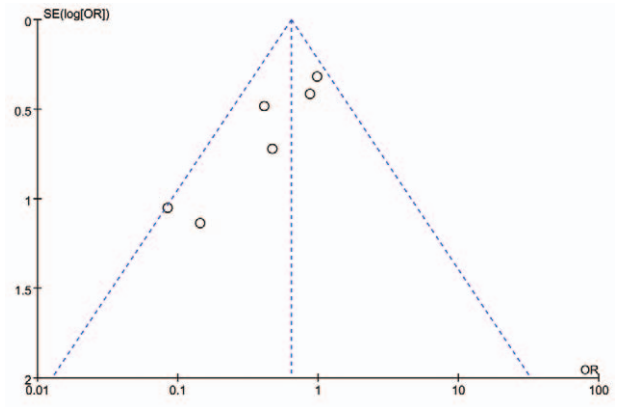

Figure 6. Funnel plot of meta-analysis.

methylprednisolone doses among the included studies, which probably contributed to the observed heterogeneity. Finally, most of the included studies were from a single site with relatively small sample sizes, resulting in a relatively small number of patients being included in this meta-analysis. Hence, multicenter studies with large sample size should be conducted.

5. Conclusions

This systematic review and meta-analysis demonstrated that methylprednisolone was safe and might reduce mortality and shorten the time of mechanical ventilation. It showed that the use of methylprednisolone was not associated with the rates of adverse events in patients with ARDS. However, well-designed and large-sample studies were required to fully characterize the efficacy and safety of methylprednisolone against ARDS.

Author contributions

Conceptualization: Hai Lv, Linfeng Dai, Mingqi Chen.
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Writing – original draft: Hai Lv, Linfeng Dai, Jun Lu, Lu Cheng, Yanxia Geng, Mingqi Chen, Qiuhua Chen, Xing Wang.
Writing – review & editing: Hai Lv, Linfeng Dai, Xing Wang.

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