

# The value of ROX index in predicting the outcome of high flow nasal cannula: a systematic review and meta-analysis

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## Research

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# Abstract

**Background:** High flow nasal cannula (HFNC) therapy is widely employed in acute hypoxemic respiratory failure (AHRF) patients. However, the techniques for predicting HFNC outcome remain scarce.

**Methods:** PubMed, EMBASE, and Cochrane Library were searched until April 20, 2021. We included the studies that evaluated the potential predictive value of ROX (respiratory rate-oxygenation) index for HFNC outcome. This meta-analysis determined sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic score, diagnostic odds ratio (DOR), and pooled area under the summary receiver operating characteristic (SROC) curve.

**Results:** We assessed nine studies with 1933 patients, of which 745 patients experienced HFNC failure. This meta-analysis found that sensitivity, specificity, PLR, NLR, diagnostic score, and DOR of ROX index in predicting HFNC failure were 0.67 (95% CI 0.57-0.76), 0.72 (95% CI 0.65-0.78), 2.4 (95% CI 2.0-2.8), 0.46 (95% CI 0.37-0.58), 1.65 (95% CI 1.37-1.93), and 5.0 (95% CI 4.0-7.0), respectively. In addition, SROC was 0.75 (95% CI 0.71-0.79). Besides, our subgroup analyses revealed that ROX index had higher sensitivity and specificity for predicting HFNC failure in COVID-19 patients from non-European countries, while the acquisition time of 6 h after receiving HFNC had a lower sensitivity and specificity when compared to other times.

**Conclusions:** This study demonstrated that ROX index could function as a novel potential marker to identify patients with a higher risk of HFNC failure. However, the prediction efficiency was moderate, and additional research is required to determine the optimal cut-off value and proper acquisition time of ROX index in the future.

## Introduction

High flow nasal cannula oxygen therapy (HFNC) is designed to supply constantly inspired oxygen concentration (21% -100%), temperature (31-37 °C), and humidity through high flow (8~80 L/min) nasal prongs. Although it is applied in clinics for only a short time, it has become a critical oxygen therapy tool for hypoxemic acute respiratory failure (ARF) patients nowadays. Several recently published studies have confirmed that HFNC is safe and effective for ARF patients<sup>[1-3]</sup>, particularly for decreasing the intubation risk. Oriol Roca<sup>[4]</sup> et al. identified that HFNC was the only variable associated with a lower risk of subsequent mechanical ventilation (MV) (odds ratio, 0.11, 95% CI, 0.02–0.69;  $P = 0.02$ ) in ARF patients. Another study demonstrated that patients with  $\text{PaO}_2/\text{FiO}_2 \leq 200$  mmHg exhibited a lower risk of intubation than standard oxygen therapy or non-invasive ventilation (NIV)<sup>[5]</sup>.

As a previous study demonstrated that delaying intubation increases mortality<sup>[6]</sup>, patients with a higher risk of HFNC failure must be carefully monitored, and intubation indications should be dynamically evaluated. However, identifying patients with a high risk of HFNC failure is a significant challenge. Higher respiratory rate and lower  $\text{PaO}_2/\text{FiO}_2$  were two predictors of intubation in ARF patients treated with non-invasive oxygenation strategy<sup>[7]</sup>, and since a great linear correlation is present between  $\text{PaO}_2/\text{FiO}_2$  and  $\text{SpO}_2/\text{FiO}_2$  parameters<sup>[8]</sup>,  $\text{SpO}_2/\text{FiO}_2$  can be an effective substitute for  $\text{PaO}_2/\text{FiO}_2$ . Based on the above principles, a new index called ROX (respiratory rate-oxygenation, calculated by the ratio of  $\text{SpO}_2/\text{FiO}_2$  to respiratory rate) was developed in recent years. Several studies thought that ROX index had a good predictive capacity for HFNC outcome<sup>[9-14]</sup>, whereas others demonstrated that ROX index should not be routinely utilized to predict HFNC outcome<sup>[15]</sup>. As a result, we created a unified standard to systematically investigate the predictive capacity of ROX index for HFNC failure.

## Methods

### Protocol and guidance

Our meta-analysis was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)<sup>[16]</sup>. The protocol of this study was registered, with PROSPERO registration number of CRD42021240607.

### Literature search strategy

According to the criteria of literature retrieval strategies, two authors independently searched MEDLINE, EMBASE, and Cochrane Library electronic databases. Since the first relevant article was published in 2016, the retrieval time was from 2016 to April 20, 2021. Without language restrictions, we conducted a search using the following terms: respiratory rate-oxygenation/ ROX/ ROX index/ ROXI and HFNC/ high-flow nasal cannula/ nasal high-flow oxygen therapy/ high-flow oxygen therapy. The study research disagreements were resolved by discussions, and when discussions failed to address the disagreements, a third author was consulted.

### **Eligibility criteria**

Literatures were selected based on the following eligibility criteria: (1) Studies evaluated the ability of ROX index in predicting HFNC outcome among adult patients (age over 18 years). (2) Number of true-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) could be found or calculated by other data from the study. (3) No restrictions were set regarding the races or locations of patients and the types of diseases for which HFNC was employed. We excluded systematic reviews, case reports, pediatric studies, and repeated reports.

### **Data extraction**

Two data collectors independently read the literatures according to inclusion and exclusion criteria and extracted the associated data elements from the enrolled papers using a self-made data extraction form. Inconsistencies were solved by discussion, and when discussion failed to address the disagreements, a third author was consulted. The extracted contents were as follows: 1) The basic characteristics of the included studies: name of the first author, publication year, locations of the study, the diseases that require HFNC use, number of patients, the study design, acquisition time of ROX index and definition of HFNC failure in each enrolled study. 2) Other essential data of each study include TP, TN, FP, FN, cut-off value of ROX index, as well as the sensitivity and specificity to predict HFNC failure. We also contacted the corresponding authors by email when necessary data were not included in the article.

### **Methodological quality assessment**

Based on quality assessment of diagnostic accuracy studies 2 (QUADAS-2) guidelines<sup>[17]</sup>, two authors independently assessed the risk of bias in enrolled studies, and a third author was invited to resolve disagreements during methodological quality assessment. The two main domains included risk of bias and applicability concerns. Each study evaluated the domain of risk of bias by evaluating patient selection, index test, reference standard, flow, and timing, whereas the domain of applicability concerns evaluated patient selection, index test, and reference standard. For each item, the risk of bias was classified as high, low, or unclear.

### **Statistical analysis**

The data analysis was conducted using STATA version 1.4 (Stata Corporation, College Station, TX). This meta-analysis determined pooled sensitivity, specificity, negative likelihood ratio (NLR), positive likelihood ratio (PLR), diagnostic score, and diagnostic odds ratio (DOR). When statistical heterogeneity was not found ( $P \geq 0.05$ ,  $I^2 \leq 50$ ), the inconsistency factor ( $I^2$ ) statistics and Cochran-Q test were employed to analyze the potential heterogeneity, and the fixed-effect model was applied to calculate the pooled effect size; otherwise, the random-effect model was utilized. Subgroup analyses were employed to explain source of heterogeneity, and they included the types of diseases associated with HFNC use, the areas of enrolled studies, and the acquisition time of ROX index. In addition, Deeks' funnel plot was performed to estimate the potential publication bias.

## **Results**

### **Literature search results**

A total of 371 literatures were searched, including 260 from PubMed, 65 from EMBASE, and 46 from the Cochrane Library databases, 3 from other sources (such as abstracts from conferences). There were 279 articles left after excluding the

reduplicated articles. After reviewing the abstracts, some articles were excluded, including systematic reviews, case reports, and coverage not matched, and 17 articles remained, which we read in full. A total of 8 studies were excluded due to the lack of data required for analysis, whereas 9 articles met the full inclusion criteria finally. The detailed PRISMA flowchart is depicted in Figure 1.

### Characteristics of the enrolled trials

The detailed baseline characteristics are demonstrated in Tables 1 and 2. All the included trials were published between 2016 and 2021. Four studies were conducted in Europe<sup>[12-15]</sup>, three in Asia<sup>[10, 11, 18]</sup>, and the remaining two in USA<sup>[9]</sup> and Africa<sup>[19]</sup>. Four studies were multiple-center<sup>[12, 13, 15, 19]</sup> and the other five were single-center studies<sup>[9-11, 14, 18]</sup>. For the types of diseases requiring HFNC use, three studies were ARF<sup>[10, 14, 15]</sup>, four were COVID-19<sup>[9, 11, 18, 19]</sup>, and two were pneumonia<sup>[12, 13]</sup>. The total number of patients was 1933, of which 745 were failure cases. Among these nine studies, five were prospective observational cohort studies<sup>[9, 10, 12, 13, 19]</sup>, three were conducted retrospectively<sup>[11, 14, 18]</sup>, and only one was RCT<sup>[15]</sup>. The acquisition time of ROX index after applying HFNC varied in different studies; six studies<sup>[9-12, 15, 19]</sup> reported 6 h as the acquisition time, one study<sup>[13]</sup> chose 12 h, another study chose 4 h<sup>[18]</sup>, and the remaining study measured ROX index before each attempt to separate from HFNC<sup>[14]</sup>. Five studies<sup>[9, 10, 12, 13, 15, 18]</sup> defined HFNC failure as the subsequent need for invasive MV, while Ming Hu et al.<sup>[11]</sup> defined HFNC failure as the need for NIV or IMV and/or death, 1 study<sup>[19]</sup> defined HFNC failure as the need for MV or death, another study<sup>[14]</sup> defined HFNC failure as requiring HFNC resumption, NIV initiation, intubation, or death. The cut-off values of ROX index ranged from 2.7 to 9.2, and while three studies<sup>[12, 13, 15]</sup> reported 4.88 as the best cut-off value, other researchers found the values of 3.66<sup>[9]</sup>, 5.55<sup>[11]</sup>, 5.8<sup>[10]</sup>, 9.2<sup>[14]</sup>, 2.7<sup>[19]</sup>, 5.31<sup>[18]</sup> in each study, and the sensitivity and specificity of ROX index to predict HFNC failure were from 50% to 84%.

### Results of methodological quality evaluation

After careful evaluation of the methodological quality of all nine enrolled studies, we found that seven studies<sup>[9, 10, 12, 13, 15, 18, 19]</sup> had a low risk of bias in patient selection, three trials<sup>[12, 13, 15]</sup> had a low risk of bias in index test, all the included studies exhibited low risk of bias in the item of reference standard, and eight studies<sup>[9-13, 15, 18, 19]</sup> had low risk in flow and timing. To sum up, the included seven studies were of good quality (Table 3).

### The meta-analysis of the ability of ROX index to predict HFNC failure

Nine trials with 1933 patients assessed the ability of ROX index in predicting HFNC outcome, and there was statistically significant heterogeneity in the sensitivity ( $I^2 = 84.97\%$ ), specificity ( $I^2 = 86.95\%$ ), PLR ( $I^2 = 33.93\%$ ), NLR ( $I^2 = 74.64\%$ ), diagnostic score ( $I^2 = 41.76\%$ ) and DOR ( $I^2 = 99.91\%$ ). Therefore, we used a random-effect model to conduct this meta-analysis. Pooling all the enrolled studies, the sensitivity, specificity, PLR, NLR, diagnostic score, and DOR of ROX index in predicting the HFNC failure are depicted in Figure 2. The pooled estimates of ROX index in predicting HFNC failure were as follows: sensitivity, 0.67 (95% CI 0.57-0.76); specificity, 0.72 (95% CI 0.65-0.78); PLR, 2.4 (95% CI 2.0-2.8); NLR, 0.46 (95% CI 0.37-0.58); diagnostic score, 1.65 (95% CI 1.37-1.93); and DOR, 5.0 (95% CI 4.0-7.0). We also conducted the summary receiver operating characteristic (SROC) plot to evaluate the predicting accuracy of ROX index (Figure 3), and the area under the curve (AUC) was 0.75 (95% CI 0.71-0.79), implying that ROX index could predict HFNC failure.

### Subgroup analyses for the predicting value of ROX stratified by different conditions

To determine heterogeneity between studies, we conducted subgroup analyses based on the types of diseases correlated with HFNC use, the areas of enrolled studies, and the acquisition time of ROX index (Table 4). For the types of diseases correlated with HFNC use, there were four trials reported data on COVID-19, with pooled sensitivity and specificity of 0.71 (0.56-0.82) and 0.73 (0.63-0.81), respectively, while lower sensitivity (0.63, 0.48-0.75) and specificity (0.71, 0.60-0.80) were found among other diseases. In the subgroup of areas of enrolled studies, the sensitivity and specificity in predicting HFNC failure were 0.64 (0.46-0.79), 0.70 (0.57-0.80) in Europe, and 0.69 (0.56-0.79), 0.74 (0.65-0.81) in the other areas. The pooled results of six enrolled

studies indicated that summary sensitivity and specificity were 0.67 (0.54-0.78) and 0.70 (0.60-0.78) when acquisition time was 6 h after receiving HFNC. However, good performance of ROX index was found in settings with other acquisition times, with sensitivity and specificity of 0.73 (0.67-0.79) and 0.74 (0.70-0.78), respectively.

### Publication bias analysis

We performed Deeks' funnel plot to evaluate the potential publication bias, and the funnel plot demonstrated no statistically significant publication bias in this meta-analysis ( $P=0.74$ ) (Figure 4).

## Discussion

The accurate prediction of HFNC outcome ensures timely detection of patients with a higher risk of intubation. This study evaluated ROX index for sensitivity and specificity in predicting HFNC failure. Our meta-analysis revealed that pooled sensitivity and specificity of ROX index were 0.67 (95% CI 0.57-0.76) and 0.72 (95% CI 0.65-0.78), respectively, the overall value of ROX index had an acceptable specificity, whereas the sensitivity was low. In the subgroup analysis, our study demonstrated that ROX index was more predictive in COVID-19 patients, the areas outside Europe, and other acquisition times (compared with 6 h after receiving HFNC). Consequently, we believed that ROX index is a promising marker to identify patients with a higher risk of HFNC failure, with a moderate prediction efficiency.

Since HFNC was first used in clinical medicine, scientists worldwide have conducted several studies on it. Since the undue delay intubation is associated with a more poor prognosis, the main concern during HFNC is the risk of intubation, and methods to early predict HFNC outcome using an accurate and easy-to-use index have recently been one of the major research hotspots. Various common respiratory (higher respiratory rate (RR)<sup>[13]</sup>, lower partial pressure of oxygen ( $\text{PaO}_2$ )/ $\text{FiO}_2$ <sup>[20-22]</sup>, the existence of thoracoabdominal asynchrony<sup>[20]</sup>) and nonrespiratory (poorly controlled diabetes<sup>[19]</sup>, hemodynamic failure<sup>[4, 21, 22]</sup>, higher Sequential Organ Failure Assessment (SOFA) score<sup>[23, 24]</sup>) factors were associated with the subsequent need for intubation or other adverse outcomes among ARF patients during HFNC. However, most of them were verified in several small sample or retrospective studies, and some other studies did not obtain similar conclusions<sup>[15]</sup>. As a result, it remains challenging to say that above-mentioned indicators can unequivocally predict HFNC outcome. Since predicting HFNC outcome is now challenging, numerous researchers investigate novel clinical variables to identify patients at high risk of HFNC failure. Among these variables, ROX index is of particular interest, especially in intensive care unit (ICU), where HFNC use has increased rapidly for years.

This meta-analysis demonstrated that ROX index could be a viable tool for clinicians to assess HFNC progress and outcome, as confirmed by many previous studies. In 2016, Oriol Roca<sup>[13]</sup> et al. firstly introduced ROX index and evaluated its value in predicting HFNC outcome. They found that ROX index effectively identified patients at lower risk of HFNC failure among pneumonia patients, and their study also indicated that ROX index had the best prediction accuracy than  $\text{SpO}_2/\text{FiO}_2$  and RR. Another study<sup>[12]</sup> further demonstrated that evaluating ROX index dynamic changes helped discriminate pneumonia patients who succeeded from patients with HFNC failure, and patients with ROX index  $\geq 4.88$  in 12th hour after the onset of HFNC have a lower risk of intubation, while the risk of HFNC failure is high if ROX index  $< 3.85$ . Besides pneumonia patients, some researchers also studied the value of the ROX index in predicting HFNC outcome among COVID-19 patients. In 2020, Abhimanyu Chandel<sup>[9]</sup> et al. conducted a multi-center, retrospective, observational study in which 272 patients with respiratory failure due to COVID-19 were enrolled. They found that ROX index higher than three was associated with HFNC success. A retrospective cohort study with 324 COVID-19 patients revealed that ROX index was an independent factor of HFNC failure when combined with thrombocytopenia and elevated IL-6 values, implying increased HFNC predictability<sup>[18]</sup>. In addition, two studies demonstrated that ROX index had a good predictive ability for HFNC outcome among COVID-19 patients<sup>[11, 19]</sup>. COVID-19 has become a global epidemic, with over one hundred million people infected and many patients treated with HFNC, many of whom required invasive ventilation during disease. The ROX index may be a simple-to-use tool for identifying COVID-19 patients at increased risk of intubation. However, a study published recently revealed that ROX index had a poor performance to predict intubation among immunocompromised patients receiving HFNC for ARF; the AUC was only 0.623 (0.557–0.689),

and when a threshold of 3.47 was utilized, the sensibility and specificity of ROX index to predict intubation were 52.1% and 68.9%, respectively. However, this was the only research that found poor ability of ROX index in predicting intubation<sup>[15]</sup>. Consequently, most trials published recently confirmed the value of ROX index in predicting HFNC outcome. Furthermore, the acquisition of ROX index was non-invasive; no blood samples from patients were required, which was especially beneficial in decreasing patient suffering. Except for the value in predicting HFNC outcome, ROX index was also studied in other aspects. In 2020, a large retrospective study that included 2862 sepsis patients found that ROX index was an independent prognostic index for 28-day mortality<sup>[25]</sup>. Similarly, Emma Prower<sup>[26]</sup> et al. demonstrated that ROX index might even outperform NEWS<sub>2</sub> (National Early Warning Score) in predicting COVID-19 deterioration. Another retrospective multi-center study published recently also found that ROX index was higher in patients experiencing successful CPAP (continuous positive airway pressure) than those who did not<sup>[27]</sup>.

This meta-analysis illustrated that prediction efficiency of ROX index was moderate, and several reasons may explain this. Firstly, the cut-off of ROX index varied in different studies, and differences in study patients may cause variation in the ideal cut-off value. Therefore, the best cut-off value of index remains controversial, and further studies are warranted to determine the best cut-off value in different populations. Secondly, although most included studies acquired the index at 6 h after receiving HFNC, the ideal time to acquire the index remains unknown, and further studies are required to find the proper time. Thirdly, the ROX index could only reflect the work of breathing, and other factors such as tachycardia were associated with HFNC failure<sup>[7]</sup>. The prediction ability of ROX index may be improved when combined with other parameters. In 2020, Ken Junyang Goh<sup>[10]</sup> et al. reported a new index called ROX-HR index (the ratio of ROX index over HR), and their study indicated that ROX-HR index higher than eight was significantly associated with HFNC success at 6 and 10 h, and ROX-HR index outperformed ROX index in predicting HFNC failure among postintubation patients. However, this was the only study that evaluated ROX-HR index value in predicting HFNC failure. Finally, the challenging problem is when to conduct intubation when ROX index is lower than the cut-off value. Should we act immediately or wait until the criteria to intubate are met completely? Obviously, studies are required to identify an optimal intubation time in the future.

Our meta-analysis has the following strengths. Firstly, to the best of our knowledge, this was the first meta-analysis to systematically assess ROX index value for predicting HFNC failure. Secondly, we conducted several meaningful subgroup analyses to comprehensively evaluate ROX index value in predicting HFNC failure, and the result of this analysis may help guide clinical practice. Thirdly, we included recently published nine studies with good quality after careful evaluation of methodological quality by two authors independently. Finally, our study strictly conformed to the broad EQUATOR guidelines-a tool to ensure the value and reliability of research literature<sup>[28]</sup>. All the advantages mentioned above contribute to the robustness and clinical value of this meta-analysis.

However, this meta-analysis also has several limitations. Firstly, most studies included had a small sample size; this may distort the results to some extent. Secondly, only one study was multicenter RCT, whereas the most were single-center prospective observational cohort studies. Thirdly, there was significant heterogeneity among the enrolled studies. Although we conducted subgroup analysis to identify the source of heterogeneity, other factors like variation in the cut-off, bias in HFNC failure definition may also be possible heterogeneity sources, which may cause practice variation. As a consequence, since findings and interpretations of this meta-analysis are limited by shortcomings showed above, it is crucial to be prudent when referencing some results of this study and must consider personal experiences and practical situations of patients.

## Conclusion

In summary, our meta-analysis reveals that ROX index is an easy-to-use and promising tool for clinicians to identify patients with a higher risk of HFNC failure, and those with a lower value of ROX index must be carefully monitored, accompanied by dynamic evaluation of intubation indications. Additional studies are required to determine the best cut-off value and the proper acquisition time of ROX index in the future.

## Declarations

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## Tables

**Table 1: Characteristics of the included studies**

Study	Country	Population	Total cases	Failure cases	Study design	Acquisition time	Definition of HFNC failure
Virginie Lemiale 2021	France+Belgium	Immunocompromised patients with ARF	302	115	RCT	6 h after receiving HFNC	The subsequent need for invasive MV
Oriol Roca 2016	Spain+France	Pneumonia	157	44	Prospective observational cohort study	12 h after receiving HFNC	The subsequent need for invasive MV
Oriol Roca 2019	Spain+France	Pneumonia	191	68	Prospective observational cohort study	6 h after receiving HFNC	The subsequent need for invasive MV
Ken Junyang Goh 2020	Singapore	Acute hypoxemic respiratory	99	45	Prospective observational cohort study	6 h after receiving HFNC	The subsequent need for invasive MV
Abhimanyu Chandel 2020	USA	COVID-19	272	108	Prospective observational cohort study	6 h after receiving HFNC	The subsequent need for invasive MV
Ming Hu 2020	China	COVID-19	105	40	Retrospective cohort study	6 h after receiving HFNC	Need for NIV or IMV and/or death
Maeva Rodriguez 2019	France	ARF	190	22	Retrospective cohort study	Before each separation attempt	Requiring HFNC resumption, NIV initiation, intubation, or death
Gregory L Calligaro 2020	South Africa	COVID-19	293	156	Prospective observational cohort study	6 h after receiving HFNC	Need for MV or death
Jiqian Xu 2020	China	COVID-19	324	147	Retrospective cohort study	4 h after receiving HFNC	The subsequent need for invasive MV

HFNC: High flow nasal cannula; ARF: Acute respiratory failure; RCT: Randomized controlled study; MV: Mechanical ventilation; NV: Noninvasive ventilation, IMV: Invasive ventilation.

**Table 2: The detailed characteristics of the included studies**

Study	TP	FP	TN	FN	Cut-off	Sen	Spe
Virginie Lemiale 2021	60	58	129	55	4.88	0.52	0.69
Oriol Roca 2016	31	31	82	13	4.88	0.70	0.73
Oriol Roca 2019	57	61	62	11	4.88	0.84	0.50
Ken Junyang Goh 2020	26	14	40	19	5.8	0.58	0.74
Abhimanyu Chandel 2020	53	26	138	55	3.66	0.49	0.84
Ming Hu 2020	34	25	40	6	5.55	0.85	0.62
Maeva Rodriguez 2019	11	27	141	11	9.2	0.50	0.84
Gregory L Calligaro 2020	106	32	105	50	2.7	0.68	0.77
Jiqian Xu 2020	114	60	117	33	5.31	0.78	0.66

TP: True positive; FP: False positive; TN: True negative; FN: False negative; Sen: Sensitivity; Spe: Specificity.

**Table 3: Methodological quality assessment of studies included**

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Virginie Lemiale 2021	LR	LR	LR	LR	LC	LC	LC
Oriol Roca 2016	LR	LR	LR	LR	LC	UC	LC
Oriol Roca 2019	LR	LR	LR	LR	LC	LC	LC
Ken Junyang Goh 2020	LR	UR	LR	LR	LC	LC	LC
Abhimanyu Chandel 2020	LR	UR	LR	LR	LC	LC	LC
Ming Hu 2020	UR	UR	LR	LR	LC	LC	LC
Maeva Rodriguez 2019	UR	UR	LR	UR	LC	UC	LC
Gregory L Calligaro 2020	LR	UR	LR	LR	LC	LC	LC
Jiqian Xu 2020	LR	UR	LR	LR	LC	LC	LC

LR: low risk; HR: high risk; UR: unclear risk; LC: low concern; HC: high concern; UC: unclear concern.

**Table 4: Subgroup analysis for the predicting value of ROX**

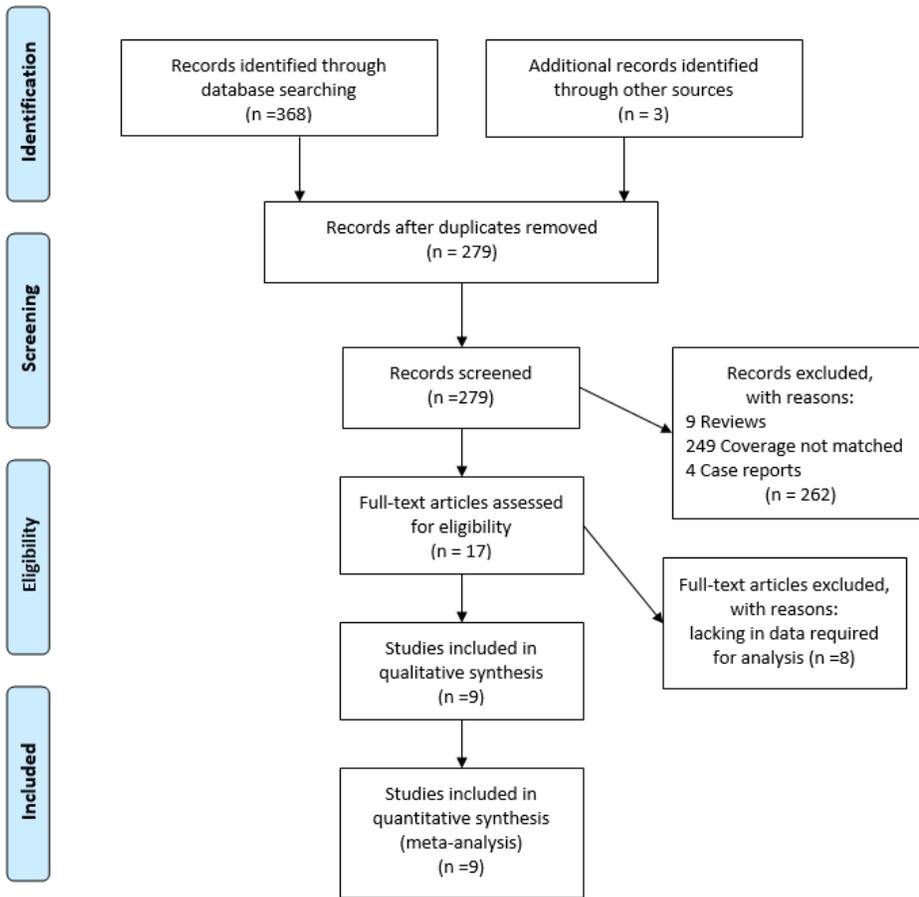
Subgroups	Number of articles	Sen	Spe	PLR	NLR	DOR	AUC
<b>Overall studies</b>	9	0.67(0.57-0.76)	0.72(0.65-0.78)	2.4(2.0-2.80)	0.46(0.37-0.58)	5(4-7)	0.75(0.71-0.79)
<b>Population</b>							
COVID-19	4	0.71(0.56-0.82)	0.73(0.63-0.81)	2.60(2.10-3.30)	0.40(0.28-0.56)	7 (5-9)	0.78(0.74-0.82)
Other population	5	0.63(0.48-0.75)	0.71(0.60-0.80)	2.10(1.70-2.70)	0.53(0.40-0.70)	4 (3-6)	0.72(0.68-0.76)
<b>Area</b>							
Europe	4	0.64(0.46-0.79)	0.70(0.57-0.80)	2.10(1.60-2.80)	0.51(0.36-0.73)	4 (3-7)	0.73(0.68-0.76)
Other areas	5	0.69(0.56-0.79)	0.74(0.65-0.81)	2.60(2.20-3.20)	0.42(0.32-0.56)	6 (5-8)	0.78(0.74-0.81)
<b>Acquisition time</b>							
6 h after receiving HFNC	6	0.67(0.54-0.78)	0.70(0.60-0.78)	2.20(1.80-2.80)	0.47(0.35-0.63)	5(3-7)	0.74(0.70-0.78)
Other time	3	0.73(0.67-0.79)	0.74(0.70-0.78)	2.84(2.39-3.39)	0.36(0.29-0.45)	7(5-10)	0.79(0.75-0.83)

Sen: Sensitivity; Spe: Specificity; PLR: Positive likelihood ratio; NLR: Negative likelihood ratio; DOR: Diagnostic odds ratio; AUC: Area under curve; HFNC: High flow nasal cannula.

## Figures



## PRISMA 2009 Flow Diagram

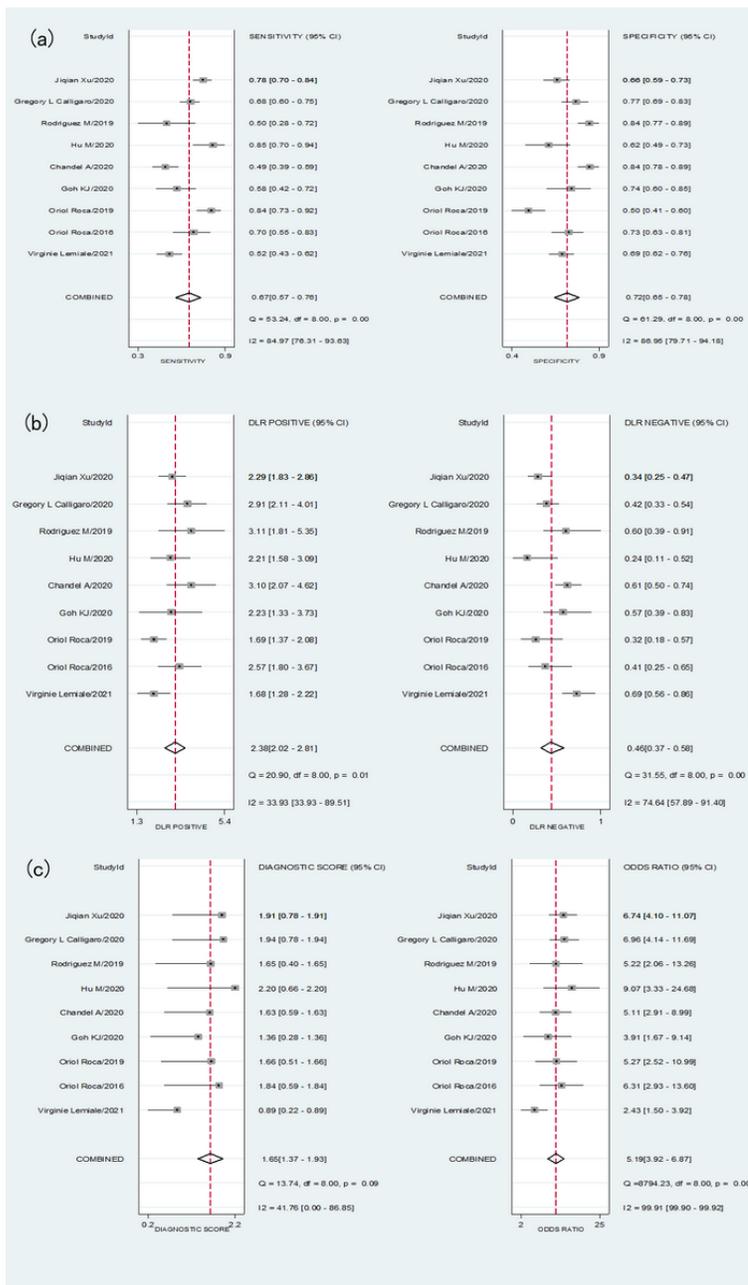


From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit [www.prisma-statement.org](http://www.prisma-statement.org).

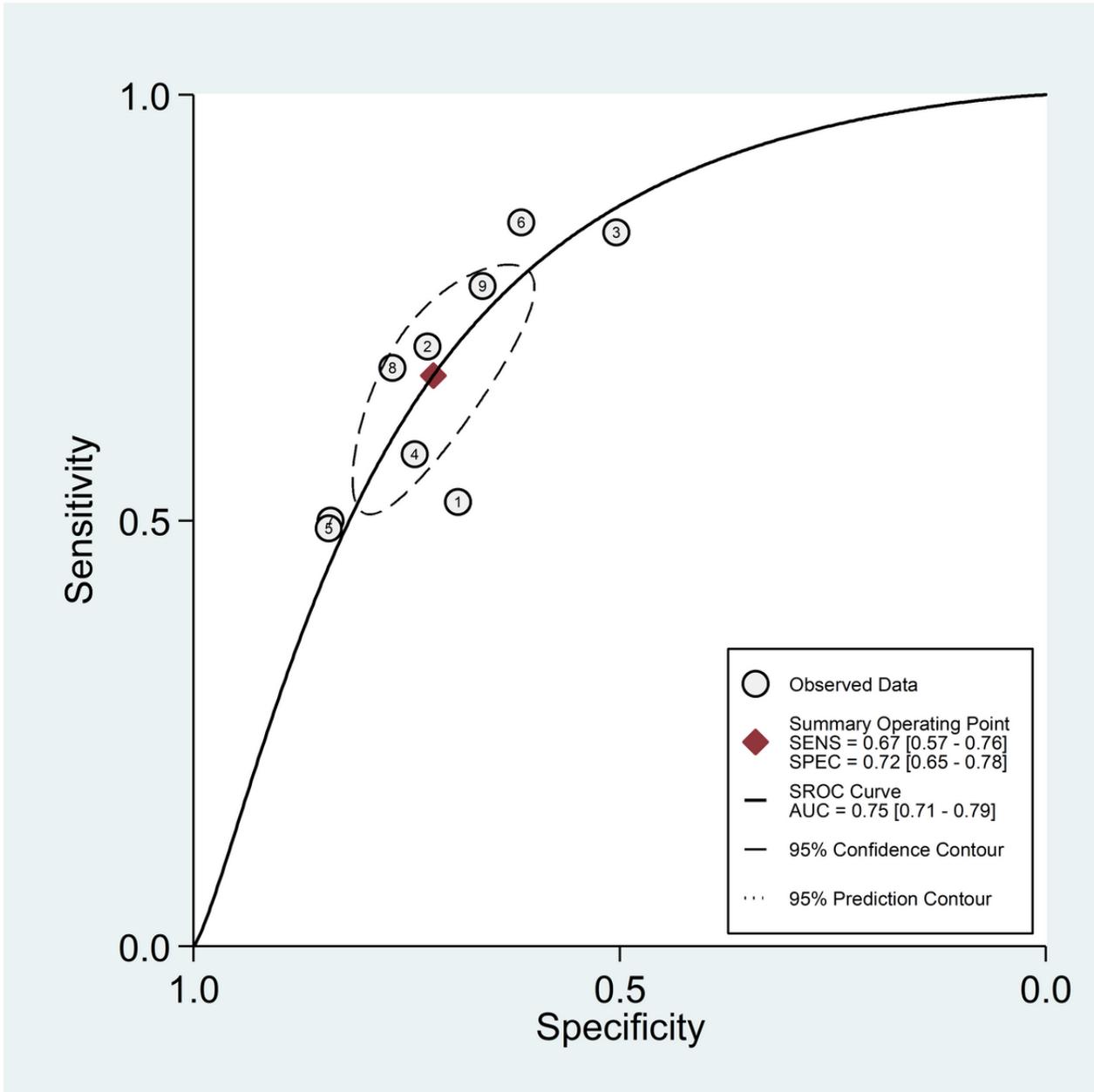
**Figure 1**

PRISMA flow diagram of the study selection process.



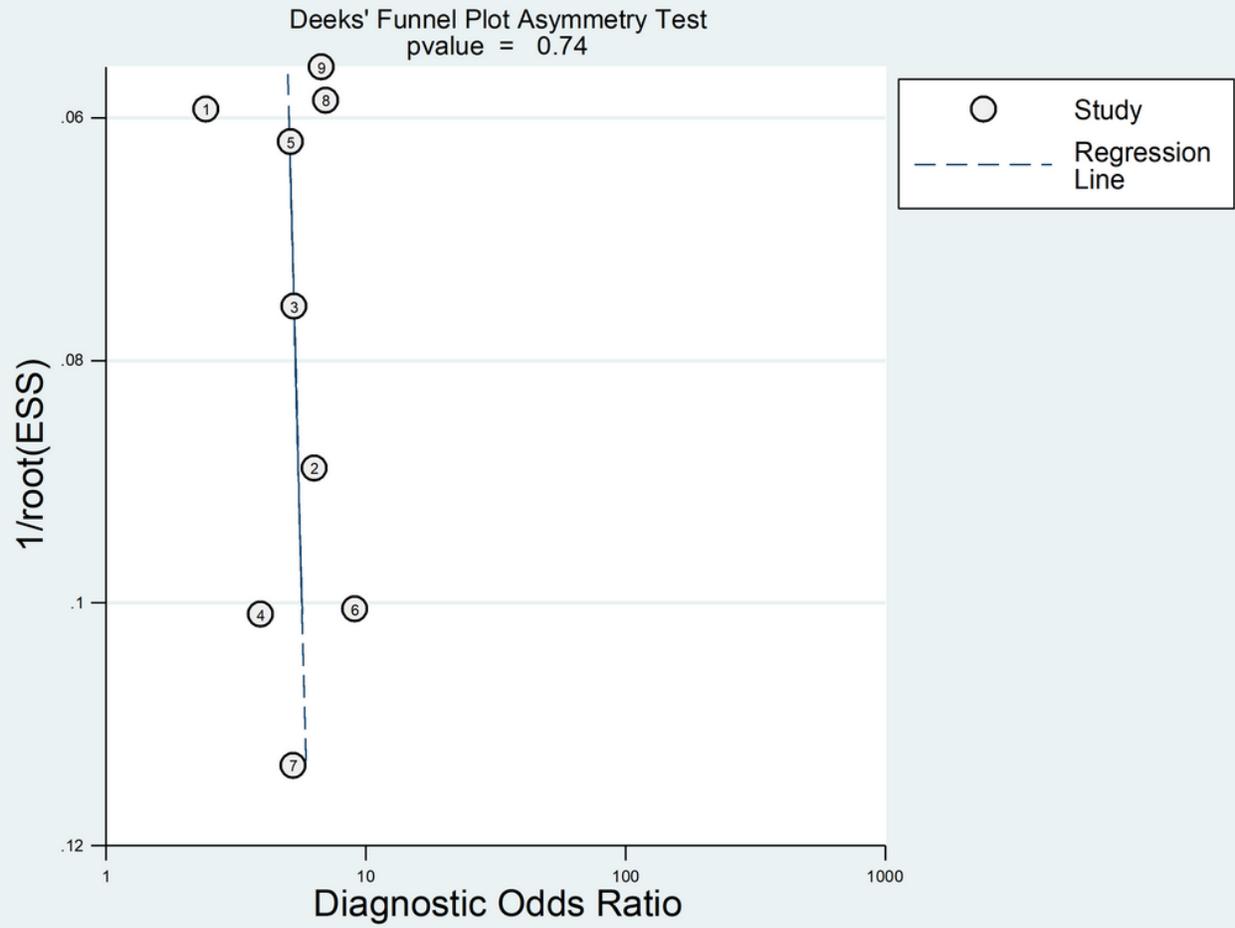
**Figure 2**

a, Forest plot of the sensitivity (SEN) and specificity (SPE) of the ROX index in predicting outcome of High flow nasal cannula (HFNC), the pooled SEN and SPE were 0.67 (95% CI 0.57-0.76) and 0.72 (95% CI 0.65-0.78), respectively. b, Forest plot of the positive likelihood ratio (PLR), negative likelihood ratio (NLR) of the ROX index in predicting outcome of HFNC, the pooled PLR and NLR were 2.4 (95% CI 2.0-2.8) and 0.46 (95% CI 0.37-0.58), respectively. c, Forest plot of the diagnostic score, diagnostic odds ratio (DOR) of the ROX index in predicting outcome of HFNC, the pooled diagnostic score and DOR were 1.65(95% CI 1.37-1.93) and 5.0 (95% CI 4.0-7.0), respectively.



**Figure 3**

The summary receiver operating characteristic (SROC) plot to evaluate the predicting accuracy of ROX index, and the area under the curve (AUC) was 0.75 (95% CI 0.71-0.79), implying that ROX index could predict HFNC failure.



**Figure 4**

The Deeks' funnel plot to evaluate the potential publication bias, this funnel plot demonstrated no statistically significant publication bias in this meta-analysis (P=0.74).