REVIEW

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A Bayesian Network Meta-Analysis Comparing Biliary Stent Types' Outcome and Complications in Unresectable Malignant Biliary Obstructions

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Abstract

Objective: To conduct a network meta-analysis (NMA) in comparing biliary stents types' outcomes and complications in unresectable MBO. **Methods:** The study was conducted in accordance with the PRISMA and NMA extension . Comprehensive searches of the Cochrane Library, MEDLINE, and Scopus were done analyzing randomized controlled trials that included subjects with unresectable malignant biliary obstructions that underwent biliary stents placement from any approaches. The types of stents that included were full-covered metal (FMS), partially-covered metal (PMS), uncovered metal (UMS), plastic (PLS), Iodine-125 seeds strands (IRS), antireflux (ARS), and paclitaxel-coated (PXS) stents. The outcome parameters were clinical success, median patency duration, medial survival, and early 30-day mortality. The complications included were stent occlusion, stent migration, cholangitis, cholecystitis, pancreatitis, hemorrhage, and hemobilia. The NMA will be done based on Bayesian method, Markov Chain Monte Carlo algorithm, using BUGSnet package in R studio. Transivity was controlled by methods and consistency of the NMA will be fitted by deviance information criterion. Data analysis in NMA were presented in Sucra plot, league table, and forest plot. **Result:** Thirty-six RCTs were included with 3502 subjects. ARS had the best clinical success and longest median patency. However, it was associated with higher rate of complications. IRS had a good clinical success (RR 1.63; 95%CI 0.67-6.25), long median patency (MD 21.14; 95%CI -106.18 to 145.91), and high significant survival rate (MD 69.89; 95%CI 22 to 117.57) compared to others stents. It was associated unsignificant complications of cholecystitis, hemobilia, and hemorrhage. **Conclusion:** Iodine-125 seeds strands had the promising good outcome and tolerated complications among others and should be considered as a standard stent to be used in unresectable malignant biliary obstructions.

Keywords: Network meta analysis- biliary stent- malignant biliary obstruction

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Introduction

Malignant biliary obstruction (MBO) diseases are challenging condition due to the inoperable at the time of diagnosis and its difficult management (Fernandez and Arvanitakis, 2019). Diagnosis is often found at an advanced stage, poorly controlled by radiotherapy and chemotherapy, which has a negative impact on the prognosis (Boulay and Birg, 2016). In this setting, biliary stenting aimed to relieve symptoms and improve quality of life (Abraham et al., 2002).

Biliary stents are usually used to restore the unidirectional flow of bile and remodel the lumen when the bile duct is occluded. Metallic and plastic stents have been emergingly used in MBOs, however in some cases, the results were not satisfactory (Jang et al., 2018). An increasing alternatives for biliary stents materials have been developed, such as irradiated, anti-reflux, and paclitaxel-coated stents.

Biliary stents placement had widely been used for palliative care in unresectable MBO. The European Society of Gastrointestinal Endoscopy guidelines recommended biliary drainage by the endoscopic route as the first choice and bypass as the second option (Polkowski et al., 2017). However, determining which was the best type of biliary stents to be used was still controversial. Until now, no head-to-head trials that compared those therapies in terms of the outcome and complications. Therefore, this study aimed to conduct a network meta-analysis in comparing biliary stents types' perfomance and complications in unresectable MBOs.

Materials and Methods

Study design

The network meta analysis (NMA) was conducted in accordance with the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols)

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in addition of NMA extension guidance. The literature search was established to address the research question phrased as follows in the PICO framework: Population (subjects with MBOs), Interventions (full-covered metal (FMS), partially-covered metal (PMS), plastic (PLS), Iodine-125 seeds strands (IRS), antireflux (ARS), and paclitaxel-coated (PXS) stents), Comparison (uncovered metal (UMS)), Outcome (clinical success, median patency duration, medial survival, and early 30-day mortality, and complications: stent occlusion, stent migration, cholangitis, cholecystitis, pancreatitis, hemorrhage, and hemobilia). Only randomized controlled trial with double-blind design was included in this study. We included all articles in the last 20 years, presented in English language, and available to be access full-text.

Study selection

Comprehensive searches of the Pubmed, Cochrane, Scopus, and MEDLINE will be done by two independent authors. All keywords related to the title and parameters of this study were searched. All studies will be inserted to End Note to filter any duplicate study. Authors read and selected the abstracts independently. All potentially eligible studies will be retrieved and full-text articles reviewed to determine eligibility. Inconsistencies will be solved by discussion among investigators. The study will be interpreted according to the GRADE Working Group approach for rating the eligible study for further analysis. A standardized electronic data form in Microsoft Excel will be used to extract the following data: author name, year of study, stent type, outcome, and complication.

Risk of bias assessment

Studies will be assessed for bias using the Cochrane risk of bias tool considering the judgment of the random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias as "Low risk" of bias, "High risk" of bias, or "Unclear risk" of bias.

Network meta-analysis

The network meta-analysis was conducted using a Bayesian method using the BUGSnetpackage of R software (https://bugsnetsoftware.github.io/). We fitted the Bayesian NMA model and generated posterior samples of parameters using the Markov chain Monte Carlo (MCMC) algorithm. The MCMC sampling was performed using the rjags package. The Bayesian framework expresses the degree of uncertainty using a probability model by applying the probability concept to the parameters.

Transitivity in this NMA will be attenuated by only including studies for which methodology and characteristics are as similar as possible. Consistency for this NMA will be evaluated by fitting the consistency and inconsistency models in deviance information criterion (DIC) between both models with smaller values indicative of a better fit and considering a difference of 5 or more as important.

In this study, the selection of fixed or random model effects was based on leverage plot. We specified the Bayesian framework with 1000 number of adaptations, 1000 burn-ins, and 10,000 iterations. Smaller value (more negative value) was defined to imply a better treatment result. In addition, we used Bayesian Markov chain MonteCarlo modeling to rank the treatments according to the surface under the cumulative ranking curve (SUCRA) probabilities. Rank 1 is considered as the best and leads to the greatest reduction in the relevant outcome,whereas rank N is the worst and is associated with higher rates of the outcome. Then, we plotted the league table or heat plot, which contained all information about relative effectiveness and their uncertainty for all possible pairs of interventions.

Results

There were 36 studies included with 3502 total subjects analyzing 7 stents, FMS, PMS, UMS, PLS, IRS, ARS, and PXS (Figure 1) (Kaassis et al., 2003; Isayama et al., 2004; Soderlund and Linder, 2006; Krokidis et al., 2010; Kullman et al., 2010; Telford et al., 2010; Krokidis et al., 2011; Song et al., 2011; Chen et al., 2012; Sangchan et al., 2012; Zhu et al., 2012; Kitano et al., 2013; Moses et al., 2013; Mukai et al., 2013; Ung et al., 2013; Hu et al., 2014; Lee et al., 2014; Walter, 2014; Yang et al., 2015; Lee et al., 2016; Hasimu et al., 2017; Jang et al., 2017; Jiao et al., 2017; Bernon et al., 2018; Chen et al., 2018; Conio et al., 2018; Jang et al., 2018; Zhu et al., 2018; Hamada et al., 2019; Yuan et al., 2019; Cho et al., 2020; Dhondt et al., 2020; Elkilany et al., 2020; Sakai et al., 2021; Tamura et al., 2021; Wang et al., 2021). There were 7 pair comparisons can be made, such as ARS vs FMS, ARS vs PLS, ARS vs UMS, FMS vs PLS, FMS vs UMS, IRS vs UMS, PLS vs PMS, PLS vs UMS, PMS vs UMS, PXS vs UMS. Others pairs could not be made due to lack of available RCTs (Figure 2).

Median survival

There were 32 studies included in the NMA of the median stent survival. IRS, FMS, UMS, and PMS showed significant longer median survival than others stent. IRS had a significant longer median survival than UMS (MD 69.89; 95%CI 22 sd 117.57) (Figure 3) (Kaassis et al., 2003; Isayama et al., 2004; Soderlund and Linder, 2006; Krokidis et al., 2010; Kullman et al., 2010; Telford et al., 2010; Krokidis et al., 2011; Song et al., 2011; Chen et al., 2012; Sangchan et al., 2012; Zhu et al., 2012; Kitano et al., 2013; Moses et al., 2013; Mukai et al., 2013; Ung et al., 2013; Hu et al., 2014; Lee et al., 2014; Walter, 2014; Yang et al., 2015; Lee et al., 2016; Hasimu et al., 2017; Jang et al., 2017; Jiao et al., 2017; Bernon et al., 2018; Chen et al., 2018; Conio et al., 2018; Zhu et al., 2018; Hamada et al., 2019; Yuan et al., 2019; Dhondt et al., 2020; Sakai et al., 2021; Wang et al., 2021).

Median patency duration

There were 32 studies included in the analysis of the median stent patency. The longest median patency obtained in ARS, PXS, and IRS. ARS had a longer median patency duration than UMS (MD 45.3; 95%CI -134 sd 227.19) (Figure 4) (Kaassis et al., 2003; Soderlund and

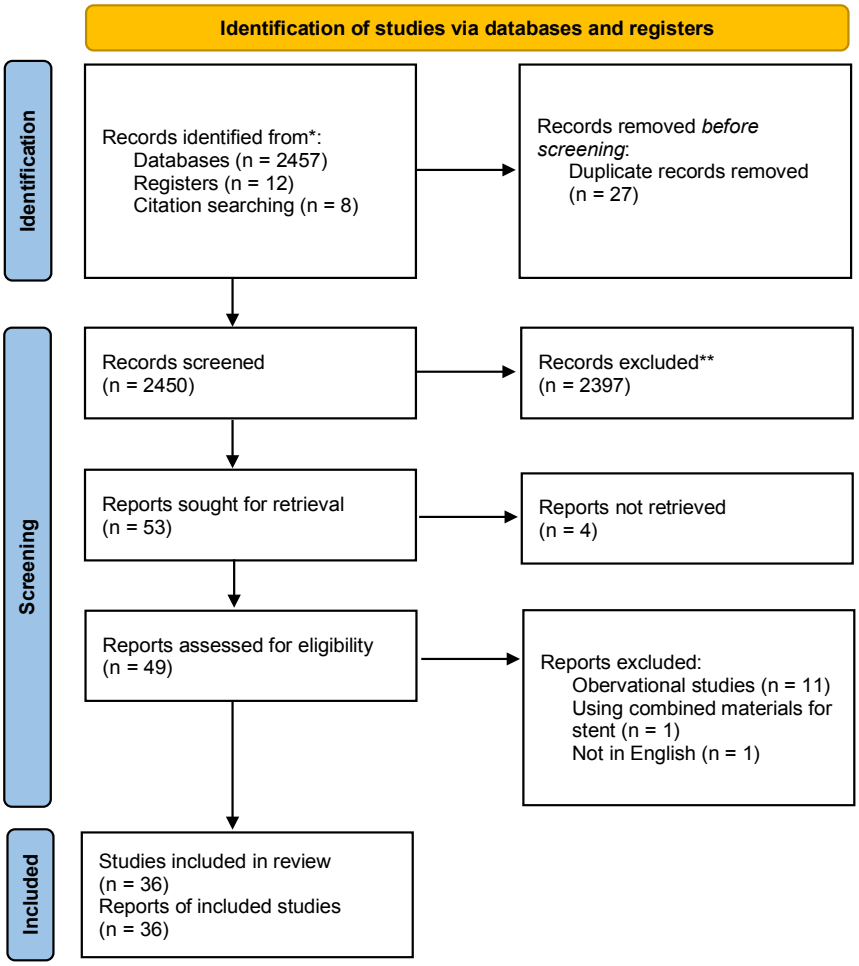

Figure 1. PRISMA diagram in this Study

Linder, 2006; Krokidis et al., 2010; Kullman et al., 2010; Telford et al., 2010; Song et al., 2011; Chen et al., 2012; Sangchan et al., 2012; Zhu et al., 2012; Kitano et al., 2013; Moses et al., 2013; Mukai et al., 2013; Ung et al., 2013; Hu et al., 2014; Lee et al., 2014; Walter, 2014; Yang et al., 2015; Lee et al., 2016; Hasimu et al., 2017; Jang et al., 2017; Jiao et al., 2017; Chen et al., 2018; Conio et al., 2018; Jang et al., 2018; Zhu et al., 2018; Hamada et al., 2019; Yuan et al., 2019; Cho et al., 2020; Dhondt et al., 2020; Sakai et al., 2021; Tamura et al., 2021; Wang et al., 2021).

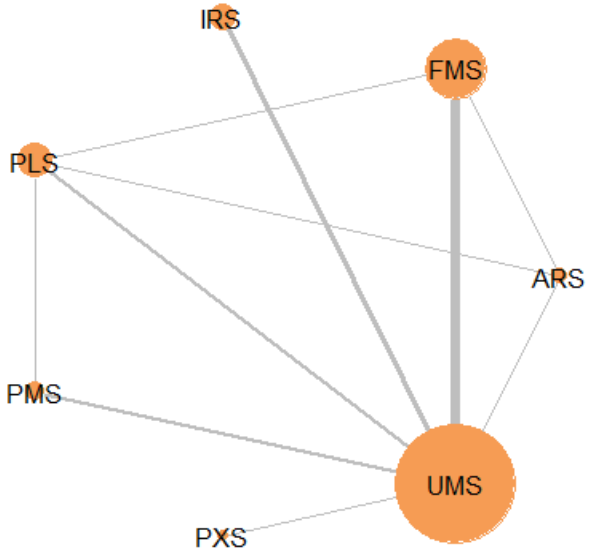

Figure 2. Network Meta-Analysis Diagram

Clinical success

There were 8 studies included in the analysis of the clinical success of the stents. No studies analyzed the clinical failure in PMS and PXS. None of the studies showed the significant clinical success compared to others. However, stents that had the highest clinical success were ARS, IRS, and UMS. ARS had a relative risk of 1.88 (95%CI 0.46-5.63) to achieve clinical success than UMS (Figure 5) (Soderlund and Linder, 2006; Sangchan et al., 2012; Hu et al., 2014; Lee et al., 2016; Zhu et al., 2018; Yuan et al., 2019; Dhondt et al., 2020; Elkilany et al., 2020).

30-day mortality

There were 7 studies included in the analysis of the rate of 30-day mortality. No study assessed the 30 day mortality of using PXS. None of the studies showed the significant 30-day mortality risk compared to others. The highest risk of 30-day mortality were found in ARS, PLS,

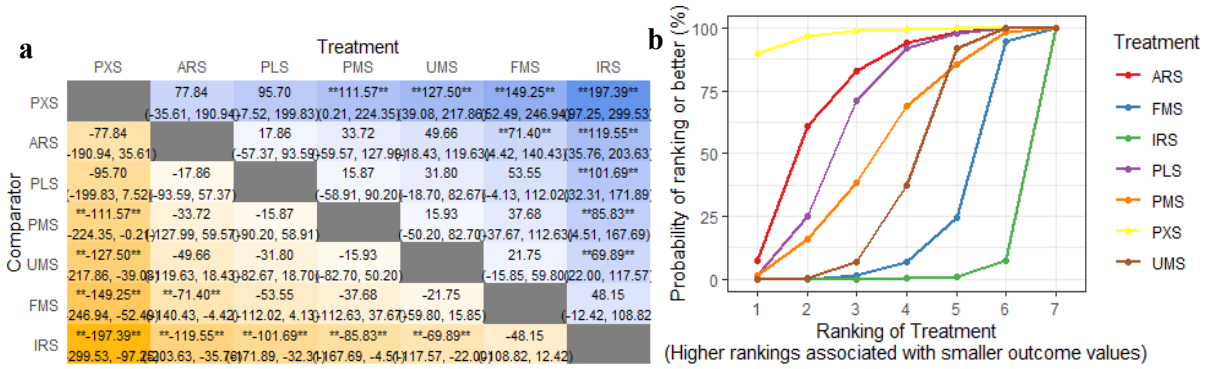

Figure 3. a, League table of the median survival, b, Probability of ranking of the median survival comparison among biliary stents types

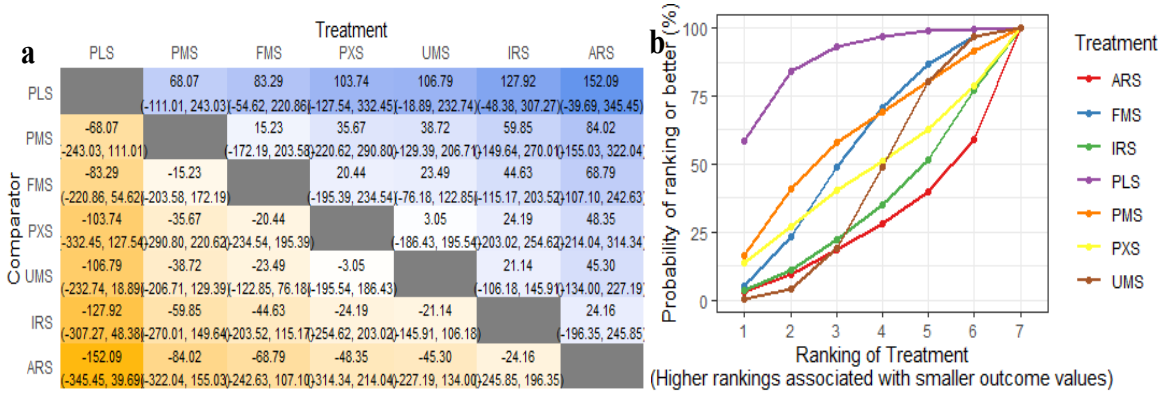

Figure 4. a, League table of the median patency duration; b, Probability of ranking of the median patency duration comparison among biliary stents types

and PMS. ARS had a relative risk of 6.6 (95%CI 0.22-33.19) in the rate of 30-day mortality than UMS (Figure 6) (Isayama et al., 2004; Sangchan et al., 2012; Zhu et al., 2012; Hu et al., 2014; Lee et al., 2016; Dhondt et al., 2020; Elkilany et al., 2020).

Intraoperative Complications

Stent occlusion

There were 29 studies included in the analysis of the rate of stent occlusion. In this study, it was shown that PLS, PXS, UMS, FMS, PMS showed significant higher relative risk to develop stent occlusion than ARS and IRS. The highest risk of stent occlusions were found in PLS, PXS, and UMS. PLS had a relative risk of 2.31 (95%CI 1.1-4.43) in developing stent occlusion than UMS (Figure 7) (Kaassis et al., 2003; Isayama et al., 2004; Soderlund and Linder, 2006; Krokidis et al., 2010; Kullman et al., 2010; Telford et al., 2010; Krokidis et al., 2011; Song et al., 2011; Chen et al., 2012; Zhu et al., 2012; Kitano et al., 2013; Mukai et al., 2013; Hu et al.,

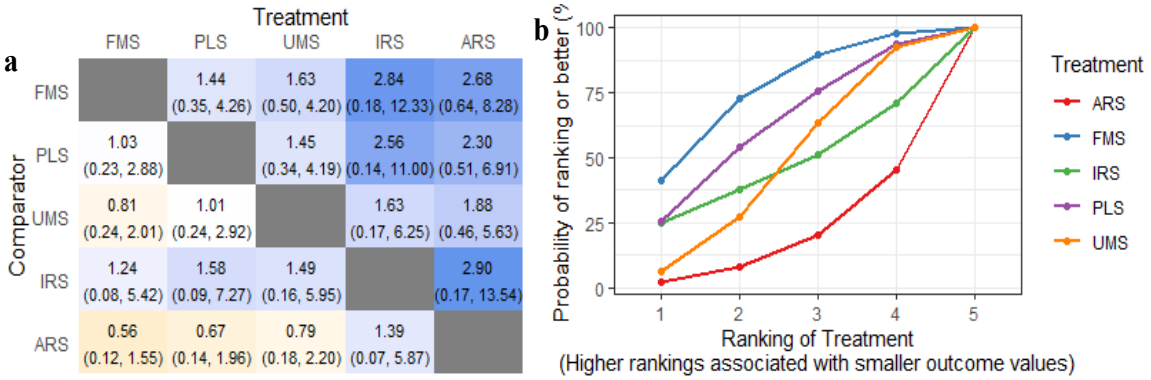

Figure 5. a, League table of the clincal success rate; b, Probability of ranking of the clinical success rate comparison among biliary stents types

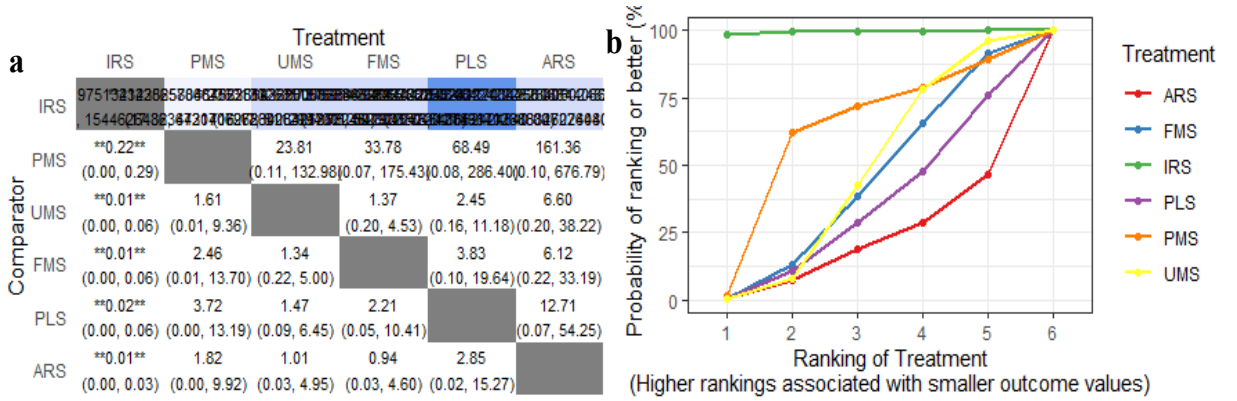

Figure 6. a, League table of the 30-day mortality rate; b, Probability of ranking of the 30-day mortality rate comparison among biliary stents types

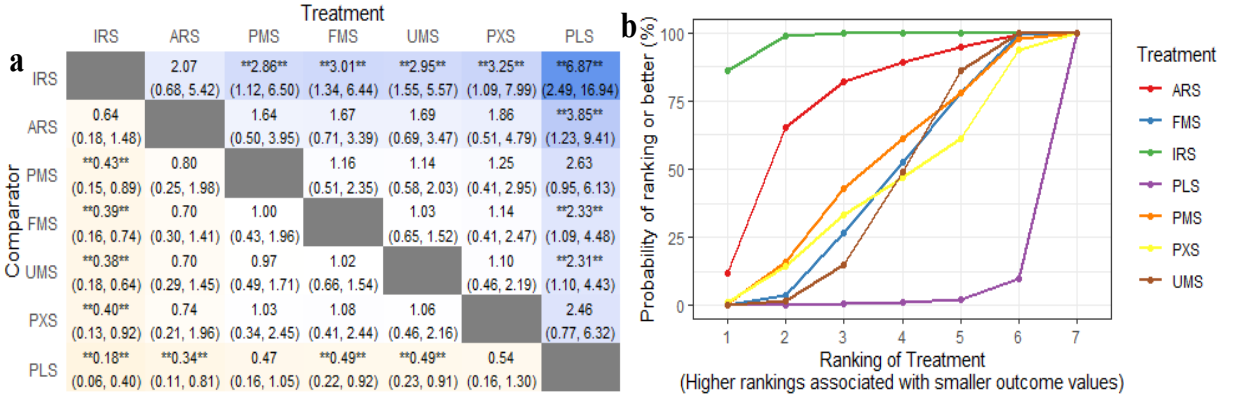

Figure 7. a, League table of the stent occlusion rate; b, Probability of ranking of the stent occlusion rate comparison among biliary stents types

2014; Lee et al., 2014; Yang et al., 2015; Lee et al., 2016; Hasimu et al., 2017; Jang et al., 2017; Jiao et al., 2017; Chen et al., 2018; Conio et al., 2018; Jang et al., 2018; Zhu et al., 2018; Dhondt et al., 2020; Elkilany et al., 2020; Sakai et al., 2021; Tamura et al., 2021; Wang et al., 2021).

Stent migration

There were 13 studies included in the analysis of the rate of stent migration. All studies except PLS and IRS showed significant higher rate of stent migration. The highest risk of 30-day mortality were found in ARS, FMS, and UMS. ARS had a relative risk of 30.91 (95%CI 0.19-127.47) in developing stent migration than UMS (Figure 8) (Isayama et al., 2004; Kullman et al., 2010; Telford et al., 2010; Zhu et al., 2012; Mukai et al., 2013; Lee et al., 2014; Hasimu et al., 2017; Jang et al., 2017;

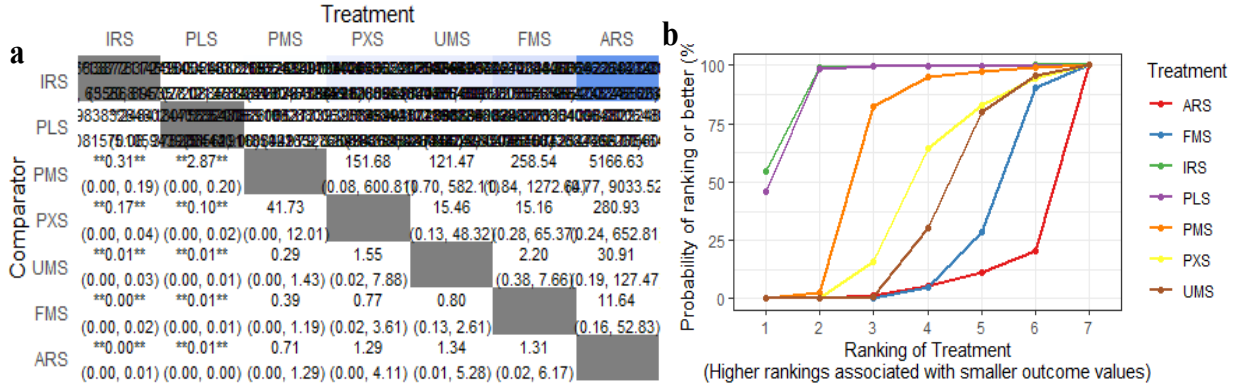

Figure 8. a, League table of the stent migration rate; b, Probability of ranking of the stent migration rate comparison among biliary stents types

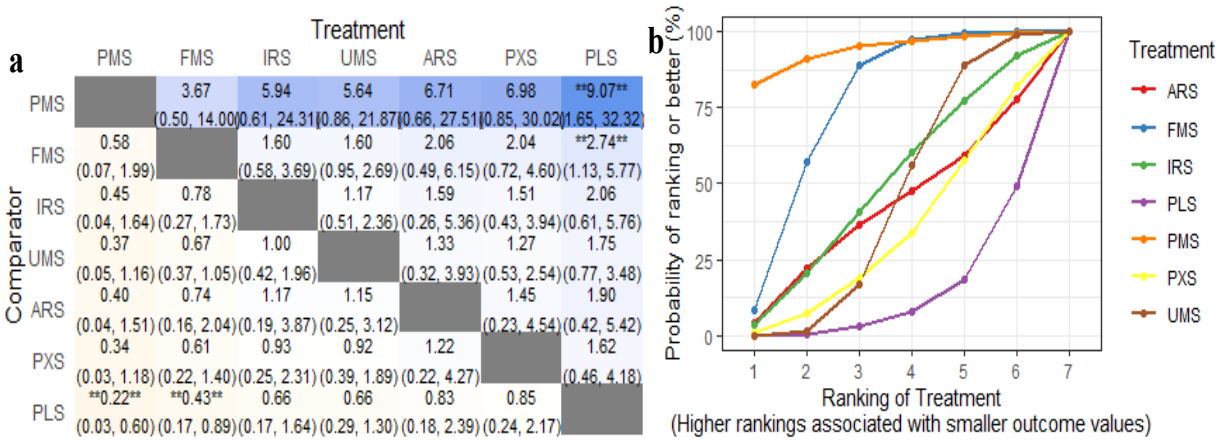

Figure 9. a, League table of the cholangitis rate; b, Probability of ranking of the cholangitis rate comparison among biliary stents types

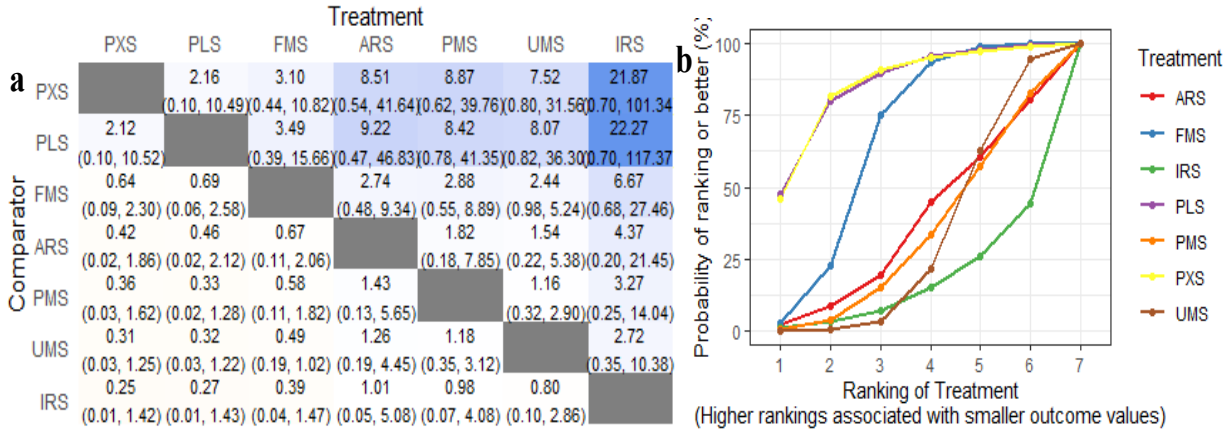

Figure 10. a, League table of the cholecystitis rate; b, Probability of ranking of the cholecystitis rate comparison among biliary stents types

Jiao et al., 2017; Conio et al., 2018; Hamada et al., 2019; Elkilany et al., 2020; Tamura et al., 2021).

Cholangitis

There were 23 studies included in the analysis of the rate of cholangitis complication. The highest risk of stent cholangitis were found in PLS, PXS, and ARS. Even, PLS showed the significant higher risk for cholangitis compared to others. PLS had a relative risk of 1.75 (95%CI 0.77-3.48) in developing cholangitis than UMS (Figure 9) (Kullman et al., 2010; Song et al., 2011; Chen et al., 2012; Sangchan et al., 2012; Kitano et al., 2013; Moses et al.,

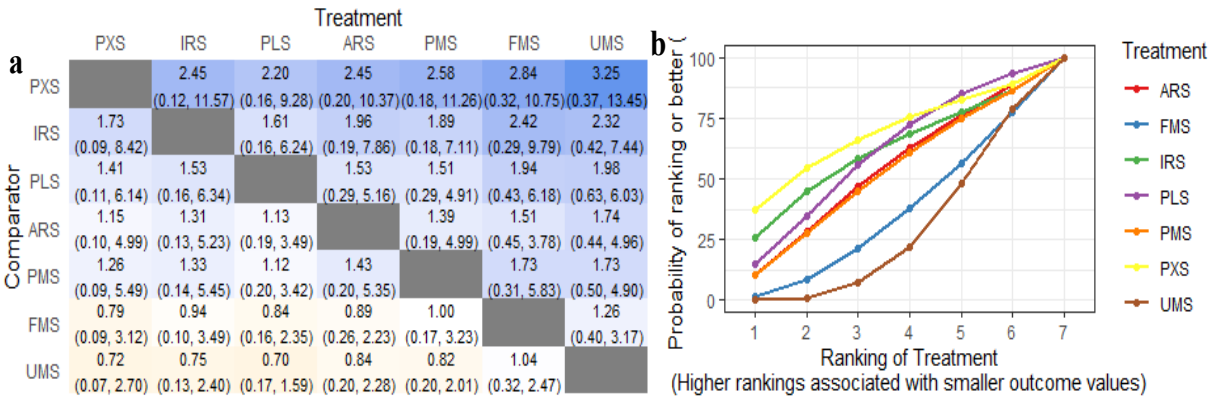

Figure 11. a, League table of the pancreatitis rate; b, Probability of ranking of the pancreatitis rate comparison among biliary stents types

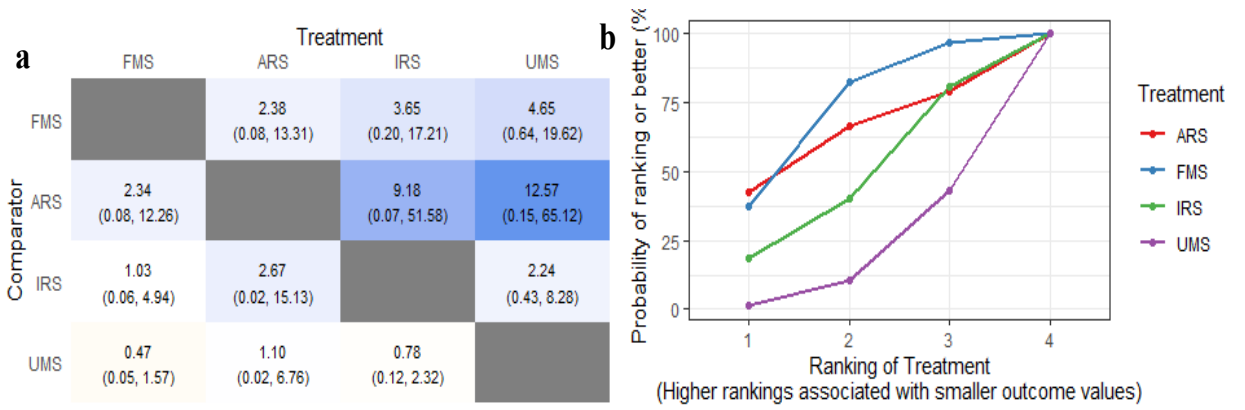

Figure 12. a, League table of the hemobilia rate; b, Probability of ranking of the hemobilia rate comparison among biliary stents types

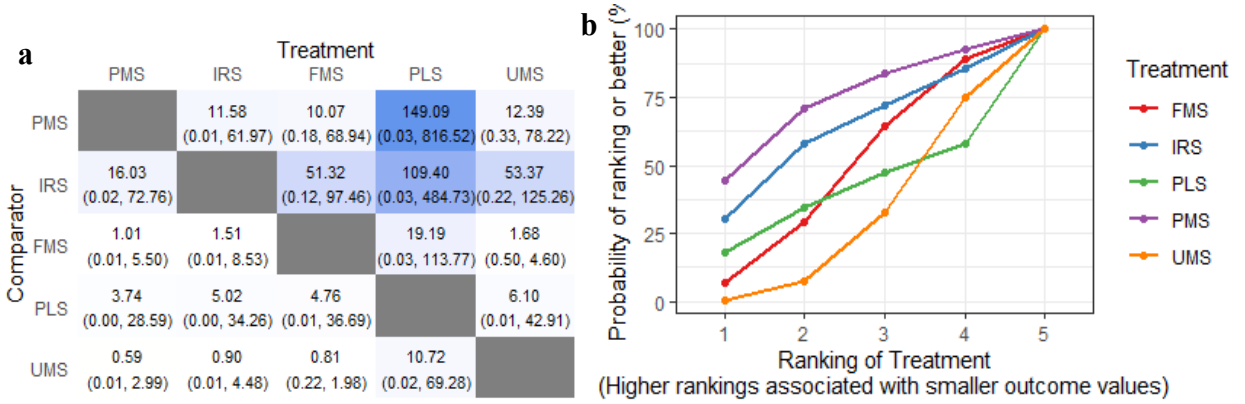

Figure 13. a, League table of the hemorrhage rate; b. Probability of ranking of the hemorrhage rate comparison among biliary stents types

2013; Ung et al., 2013; Hu et al., 2014; Yang et al., 2015; Lee et al., 2016; Hasimu et al., 2017; Jang et al., 2017; Jiao et al., 2017; Chen et al., 2018; Conio et al., 2018; Jang et al., 2018; Zhu et al., 2018; Hamada et al., 2019; Yuan et al., 2019; Dhondt et al., 2020; Elkilany et al., 2020; Sakai et al., 2021; Tamura et al., 2021).

Cholecystitis

There were 20 studies included in the analysis of the rate of cholecystitis complication. None of the studies showed the significant cholecystitis risk compared to others. The highest risk of cholecystitis were found in IRS, ARS, and PMS. IRS had a relative risk of 2.72 (95%CI 0.32-10.38) in developing cholecystitis than UMS (Figure 10) (Isayama et al., 2004; Krokidis et al., 2010; Telford et al., 2010; Krokidis et al., 2011; Kitano et al., 2013; Moses et al., 2013; Mukai et al., 2013; Ung et al., 2013; Hu et al., 2014; Lee et al., 2014; Yang et al., 2015; Jang et al., 2017; Jiao et al., 2017; Conio et al., 2018; Jang et al., 2018; Hamada et al., 2019; Elkilany et al., 2020;

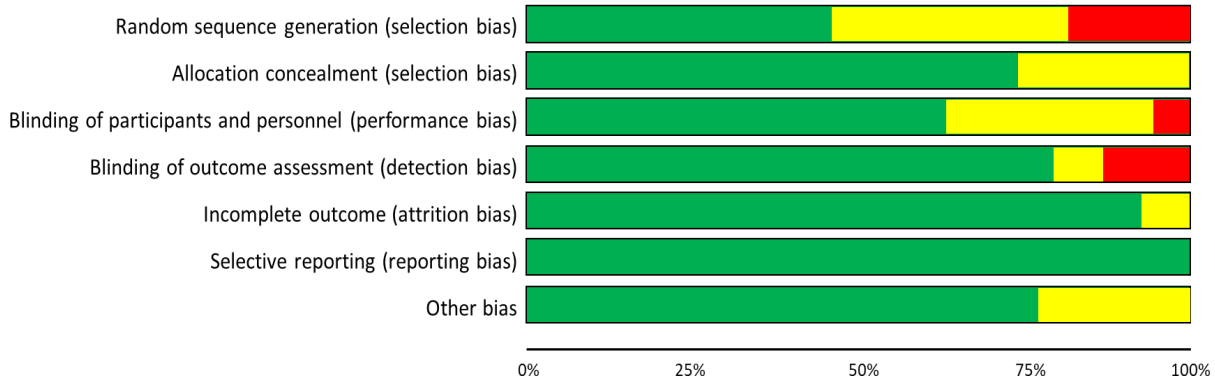

Figure 14. Bias assessment

Sakai et al., 2021; Tamura et al., 2021).

Pancreatitis

There were 21 studies included in the analysis of the rate of pancreatitis complication. None of the studies showed the significant pancreatitis risk compared to others. The highest risk of pancreatitis were found in all metal stents, UMS, FMS, and PMS. UMS had a relative risk of 1.26 (95%CI 0.4-3.17) in developing pancreatitis than FMS (Figure 11) (Isayama et al., 2004; Krokidis et al., 2010; Kullman et al., 2010; Telford et al., 2010; Song et al., 2011; Sangchan et al., 2012; Kitano et al., 2013; Moses et al., 2013; Mukai et al., 2013; Ung et al., 2013; Hu et al., 2014; Lee et al., 2016; Hasimu et al., 2017; Jang et al., 2017; Jiao et al., 2017; Zhu et al., 2018; Hamada et al., 2019; Yuan et al., 2019; Elkilany et al., 2020; Sakai et al., 2021; Tamura et al., 2021).

Hemobilia

There were 8 studies included in the analysis of the rate of hemobilia. The stents that were being analyzed only FMS, UMS, ARS, and IRS. None of the studies showed the significant higher hemobilia compared to others. The highest risk of hemobilia were found in UMS, IRS, and ARS. UMS had a relative risk of 4.65 (95%CI 0.64-19.62) in developing hemobilia than FMS (Figure 12) (Krokidis et al., 2011; Zhu et al., 2012; Lee et al., 2016; Jiao et al., 2017; Zhu et al., 2018; Hamada et al., 2019; Dhondt et al., 2020; Elkilany et al., 2020).

Intraoperative Complications

Hemorrhage

There were 9 studies included in the analysis of the rate of hemorrhage. The stents that were being analyzed only FMS, PMS, UMS, IRS, and PLS. None of the studies showed the significant higher hemorrhage compared to others. The highest risk of hemorrhage were found in PLS, UMS, and IRS. UMS had a relative risk of 1.68 (95%CI 0.01-42.91) in developing hemorrhage than FMS (Figure 13) (Isayama et al., 2004; Kullman et al., 2010; Sangchan et al., 2012; Kitano et al., 2013; Ung et al., 2013; Yang et al., 2015; Chen et al., 2018; Dhondt et al., 2020; Sakai et al., 2021).

Risk of bias assessment

The risk of bias assessment could be seen in Figure 14, that this study included studies with low risk of bias.

Discussion

MBOs are among the most lethal diseases worldwide in spite of the robust improvement in the management (GBD, 2018). For palliative setting, stent insertion is the gold standard to relieve biliary obstructions and improve quality of life (Glazer et al., 2014). It plays an important role in maintaining disease condition, decreasing complications, and mortality (Boulay and Birg, 2016).

There are many types of materials currently being used. Therefore, many doubts are raised as to which one is the most beneficial to the patient. The routinely used stent are plastic stents (PS) and self-expanding metal stents (SEMS) (Lee et al., 2016). Recently, there have been significant advancements in the development of stent from another materials, offering several options to surgeon. This NMA encompasses the materials currently used for biliary stents in the terms of outcomes and complications (Choudhury et al., 2022).

In this NMA, it was shown that ARS had the best clinical success rate (RR 1.88; 95%CI 0.46 to 5.63 than UMS) and longest median patency duration (MD 45.3; 95%CI -134 to 227.19 than UMS) compared to others stents. However, it was associated with higher rate of early 30-day mortality, stent migration, cholecystitis, hemobilia, and cholangitis complications. The second best stent with a good clinical success, long median patency duration, and high survival rate was IRS. IRS had a good clinical success, long median patency duration, and high significant survival rate (MD 69.89; 95%CI 22 to 117.57 than UMS). It was associated with lower complications, only unsignificant but higher rate of cholecystitis, hemobilia, and hemorrhage complications relative to others stents. Surprisingly, this network meta analysis showed that UMS can be considered also due to its good clinical success and high survival rate. Despite, it was associated with higher complications of stent occlusion, stent migration, pancreatitis, hemobilia, and hemorrhage. From all stents, PLS and ARS showed the higher rate of complications. Even, PLS showed significant higher rate of stent occlusion and cholangitis relative to others stents.

Iodine-125 seed strands had been shown to had small size, deliver high doses of radiation, and conformal radiotherapy with a promising advantages. It had been used widely in brachytherapy for cancers and this study proved that it was well-applied in unresectable malignant biliary obstructions (Wei et al., 2021). The complication rates of IRS was still in the tolerable rates. In other hand, we did not recommend PLS due to its higher rate of complications. Even, PLS showed significant higher rate of stent occlusion and cholangitis relative to others stents.

The only network meta-analysis comparing stents for palliative state of extrahepatic MBO was conducted by Park et al. in 2021. They recommended the use for metal stent as the first option stent to be chose for extrahepatic MBO. However, in that study, they only compared three types of stent materials, covered, uncovered, and plastic stents (Park et al., 2021). In this study, we compared 7 stents materials. Thus, this study offered the results of relative efficacy among all existed biliary stent materials, providing a better understanding and judgment for clinicians to determine which stent to be used. This remarks that this study is the first to comprehensively compare seven types of stents for the endoscopic drainage of MBO.

Nevertheless, this NMA has some limitations. First is excluding the non-English language articles. Second is the lack of consideration of patient's performance status as it was not stated in all collected studies. However, this was the first NMA that included newly designed biliary stents in network meta-analysis.

In conclusion, Iodine-125 seeds strands had the

promising good outcome and tolerated complications among others and should be considered as a standard stent to be used in unresectable malignant biliary obstructions. Future multicenter RCTs were needed to strenghten the meta analysis results.

Author Contribution Statement

All authors contributed equally in this study.

Acknowledgements

The authors acknowledged the Digestive Surgery Division which has indirectly contributed to the success of this study.

Availability of data

Data were available upon request by contacting the coressponding authors.

Conflict of interest

The authors declared that there was no conflict of interest in this study.

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