Hepatic sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) primary prophylaxis in patients undergoing hematopoietic stem cell transplantation: a network meta-analysis of randomized clinical trials

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Abstract

Introduction: Hepatic sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) is a major complication following hematopoietic stem cell transplantation, resulting from immune and chemical toxicity to the sinusoidal endothelium and hepatocellular damage. In most severe cases, multiorgan dysfunction occurs, so it is essential to promptly identify patients at greater risk of SOS/VOD and to adopt prophylactic strategies.

Objectives: This study aims to systematize the impact of different approaches as primary prophylaxis of SOS/VOD in patients undergoing hematopoietic stem cell transplantation (HSCT).

Methods: A systematic review and meta-analysis of randomized clinical trials evaluating different strategies for primary prophylaxis of SOS/VOD was carried out in a pairwise fashion and with a consistent network structure. The odds ratio (OR) and corresponding confidence intervals were calculated using the random-effects model. Heterogeneity was assessed by the I^2 method and the efficacy of each approach was estimated by SUCRA (surface under the cumulative ranking curve).

Results: Considering all patients undergoing HSCT, ursodeoxycholic acid (UDCA) [OR=0.38, 95%CI 0.14-1.06, SUCRA=0.720] was associated with a lower incidence of VOD while defibrotide reached a modest reduction in its incidence [OR=0.64, 95%CI 0.23-1.67; SUCRA=0.486]. Considering the subgroup of patients undergoing hematopoietic progenitors allotransplantation, defibrotide scored higher [OR=0.51, 95%CI 0.09-2.85, SUCRA=0.650], by comparison with UDCA [OR=0.53, 95%CI 0.14-1.96, SUCRA=0.639].

Conclusion: This is the first meta-analysis comparing primary prophylaxis of SOS/VOD. UDCA yielded more promising results when considering all patients undergoing hematopoietic stem cell transplantation, although, in a subgroup analysis of the ones exposed to allogeneic grafts, it becomes not significantly overrun by defibrotide.

1. Introduction

Sinusoidal obstruction/veno-occlusive syndrome (SOS/VOD) associated with hematopoietic stem cell transplantation has an incidence that ranges from 5%(1) to 20%, being tendentiously higher in infants and young adults (2). Its pathophysiology is representative of the conditioning regimen off-target toxicity, namely endothelial dysfunction, due to the damage inflicted upon endothelial cells and hepatocytes from zone 3 of the hepatic acinus. Briefly, chemotherapeutic agents and radiotherapy induce the activation and

damage of endothelial cells; while the fenestration of this barrier promotes the translocation of blood figurate elements and cellular debris towards the space of Disse. These morphophysiological changes, and, the translocation of microbial-derived products coupled with the immune-reconstitution paradox after hematopoietic stem cell transplantation may further exacerbate the sinusoidal and acinar changes (3). On the other hand, the secretion of cytokines and vasoactive mediators triggers the activation of the coagulation cascade, with the deposition of clotting factors (von Willebrand factor, factor VIII, and fibrin) and vascular tamponade, further obstructing sinusoidal flow (4). Ultimately, severe SOS/VOD represents a potentially life-threatening condition, evolving from post-sinusoidal portal hypertension and liver dysfunction to multi-organ failure and death (5).

This complication is more likely to occur when certain factors are present during allogeneic hematopoietic stem cell transplantation. These factors include using donors who are not related or have mismatched HLA, using intensive conditioning treatments like busulfan-based regimens or total-body irradiation, and using grafts that haven't undergone T-cell depletion. Similarly, the presence of metabolic syndrome, iron overload, pre-existing hepatopathies (cirrhosis, history of viral hepatitis), or hemoglobinopathies (thalassemia) also increases the risk of SOS/VOD(6), as well as previous exposure to therapies with highly hepatotoxic agents, as in the case of gemtuzumab ozogamicin (7) and inotuzumab ozogamicin (8). Other factors impacting general hemostatic and redox balances also favor SOS/VOD, which itself leads to the consumption of natural circulating anticoagulants such as protein C, S, and antithrombin III (9)(10). Heparanase, an endoglycosidase that cleaves heparan sulfate (HS), also accounts for the burden of disease, with some polymorphisms significantly increasing the risk of SOS/VOD in the first 100 days after allogeneic HSCT (11).

The definition of SOS/VOD has evolved over time, ultimately relying on clinical and analytical parameters. The modified Seattle criteria defines SOS/VOD occurring in the first three weeks after HSCT when at least two of the following criteria are present: bilirubin>2mg/dL; hepatomegaly and/or right upper abdominal quadrant pain and a weight gain of at least 2% by comparison with baseline (12). The Baltimore criteria diagnosis SOS/VOD when in the first 21 days post-HSCT the serum bilirubin is higher than 2 mg/dL, and at least two other clinical findings occur, namely, hepatomegaly, ascites or weight gain (over 5% by comparison with pre-HSCT status) in the absence of an alternative medical explanation (13). However, classical definitions of SOS/VOD do not contemplate the cases diagnosed beyond the first 21 days after HSCT, which although rarer, are now defined as late-onset SOS/VOD. The European Society for Blood and Marrow Transplantation revised criteria adopted the Baltimore definition for classical SOS/VOD and, in patients beyond 21 days after HSCT, admitted that it can be defined histologically or when there is evidence of reduced or reversed portal flow coupled with at least two additional criteria (bilirubin ≥ 2 mg/dL, painful hepatomegaly, ascites or weight gain higher than 5% from baseline) (14).

In this review and meta-analysis, we delve into the randomized clinical trials (RCT) exploring primary prophylactic strategies for SOS/VOD in patients who underwent HSCT. By pooling data retrieved from different RCTs, we ranked the efficacy of different strategies, herein proposing a hierarchization of

therapeutic strategies to be adopted according to the patient's physiological reserve and transplantation protocol.

2. Methods

2.1 Literature search

The research study adhered to the Cochrane collaboration guidelines for systematic reviews (15). The search was performed in MEDLINE (https://pubmed.ncbi.nlm.nih.gov), SCOPUS (https://www.scopus.com) and Web of Science (https://www.webofknowledge.com). All relevant data was gathered from the inception of the databases up to 16th September of 2023, using the following medical subject heading terms: ["Hepatic Veno-Occlusive Disease" or "Sinusoidal obstruction syndrome"] and ["prophylaxis" or "prevention"]. The reference lists of the included studies were analyzed to search for additional studies.

2.2 Eligibility criteria

We aimed to identify all relevant publications focusing on RCT assessing the efficacy of strategies as primary prophylaxis of SOS/VOD in patients undergoing hematopoietic stem cell transplantation. Only scientific publications that fulfilled the inclusion criteria were analyzed: 1) RCT addressing primary prophylaxis regimens directed to SOS/VOD in HSCT recipients; 2) including patients who had initiated the therapeutic regimen before or at least concomitantly with the conditioning regimen and 3) studies reporting the incidence of SOS/VOD.

The exclusion criteria were being non-randomized clinical trials, post-hoc analysis comparing therapeutic interventions started after conditioning initiation, being observational studies, case reports, narrative reviews, experimental studies in basic science/translational domain, guidelines, editorials, correspondences, and consensus/expert statements.

2.3 Data collection

Two authors conducted separate reviews of titles and abstracts from studies identified through electronic searches, excluding those that did not clearly meet the eligibility criteria. The full texts of the remaining articles were then assessed to decide their inclusion or exclusion, being the list of studies selected for inclusion by each author compared, and disagreements solved by discussion until consensus.

The following information was abstracted from each study into a data extraction form: type of transplant and conditioning regimen, SOS/VOD defining criteria, and incidence of SOS/VOD in different treatment groups. Differences in data extraction were settled by consensus.

2.4 Quality assessment

The studies' methodology and reporting quality were assessed independently by authors using the Critical Appraisal Skills Programme (CASP) checklist for RCT. Furthermore, an analysis of potential bias across the studies was performed by examining funnel plots to identify any signs of asymmetry.

2.4 Statistical analysis

Only RCTs were included in this meta-analysis. Placebo and best supportive care arms were considered as a standard care treatment in our analysis, given the absence of any further pharmacological intervention approved for this indication.

Firstly, a pairwise meta-analysis was conducted comparing the prophylactic interventions following a random-effects model to estimate pooled OR (odds ratio) and 95% confidence intervals (CI). Statistical heterogeneity was assessed by the I^2 method. Secondly, a network meta-analysis operated under a consistency model using the Markov chain Monte Carlo (MCMC) method was performed, combining direct and indirect evidence for any given pair of treatments. After model optimization and non-informative prior withdrawal, posterior distributions were obtained using 3.5×10^5 iterations after 10×10^4 burns, with a thinning interval of 5. By comparing the odds of SOS/VOD development under each therapeutic regimen by comparison with the standard of care, and counting the proportion of iterations in the MCMC method in which each intervention had the lowest OR, we ranked treatments following the SUCRA (surface under the cumulative ranking curve) method. The higher the SUCRA, the higher the efficacy of the intervention (16).

The pooled analysis was performed considering all patients submitted to hematopoietic stem cell transplantation and thereafter followed by a subgroup analysis considering only the patients submitted to allogeneic hematopoietic stem cell transplantation (either treated with related or unrelated donors' grafts).

Statistical analyses were performed using the netmeta (17) and GEMTC (18) packages for R, version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria). A p-value less than 0.05 was considered

statistically significant and 95% confidence intervals were traced whenever possible to assess significance.

3. Results

3.1 Selection of studies and quality analysis

After removing duplicates, our search yielded 549 articles. These articles were evaluated based on their titles and abstracts, leading to the exclusion of those that did not meet the inclusion criteria. Subsequently, 35 articles underwent a comprehensive evaluation, resulting in the inclusion of 11 studies in the systematic review and 10 in the meta-analysis. (**Figure 1**). Among all studies included in the systematic review, ten compared a specific therapeutic intervention with placebo or best supportive care; while one specific trial compared heparin versus heparin in association with UDCA.

The overall quality of studies was classified as moderate concerning the Comprehensive Assessment of Study Protocols (CASP) for clinical trials amendment (**Figure 1, supplementary materials**). Publication bias was excluded by visual inspection of funnel plots (**Figure 2, supplementary materials**).

3.2 Characteristics of the randomized clinical trials

Table 1 summarizes the characteristics of RCTs approaching primary prophylactic regimens for SOS/VOD in the context of hematopoietic stem cell transplantation. Overall, eleven studies were included in the systematic review and ten in the meta-analysis (of whom nine were eligible for the consistency model). Concerning the studies included in the meta-analysis, four approached the role of ursodeoxycholic acid (19, 20, 21, 22), two the role of heparin (23, 24), one the role of fresh-frozen plasma (25), two the role of defibrotide (26, 27) and one the role of N-acetyl-L-cysteine (28). Overall, the studies included in the meta-analysis aggregate the data of 1795 patients and 6 different therapeutic approaches. In the glycyl-L-glutamine trial (29) there was an absence of events in both treatment and control groups.

The trial addressing the primary prophylaxis with fresh frozen plasma (FFP), although evaluated in the pairwise comparison, was withdrawn from the Bayesian analysis given the absence of events in the experimental arm. The decision was made given that such a finding would lead to an overestimation of FFP efficacy $\left[\lim_{Odds\ FFP \to 0} \left(\frac{Odds\ prophylactic\ comparator}{Odds\ FFP} \right)^{\square} = +\infty \right]$, a finding corroborated by the model fit optimization protocol accordingly to the leverage versus square root of residual deviance plot (**Figure 3, supplementary materials**).

Considering all patients that had undergone hematopoietic stem cell transplantation (either allogeneic or autologous), network estimates were pooled considering direct and indirect evidence. Although for five comparisons the pooled estimates are retrieved entirely by direct evidence, ten indirect comparisons are made and entirely based on indirect evidence. The comparator arms UDCA *versus* UDCA plus heparin, N-acetyl-L-cysteine *versus* UDCA plus heparin, and defibrotide *versus* UDCA plus heparin have to be interpreted with caution given a mean path length in network estimate higher than 2 (**Figure 4, supplementary materials**).

A subgroup analysis including only patients with allogeneic transplantation of hematopoietic progenitors pooled the data of 759 patients. The former count excluded patients enrolled in the trial comparing heparin versus UDCA plus heparin, which due to node splitting in our network model induced an impossibility to either directly or indirectly become compared with other prophylactic approaches, herein being excluded from the meta-analysis. Three network estimates were retrieved from direct evidence and the other three from indirect ones. No mean path lengths higher than 2 were retrieved in network estimates upon a random-effects model (**Figure 5, supplementary materials**).

Table 1: Summary of randomized clinical trials assessing the outcome of prophylactic regimens in SOS/VOD

Experimental Arm	Cell therapy	Population	Intervention	Control	SOS/VOD Criteria	Reference
UDCA	AlloHSCT (related donor)	67 patients submitted to allogeneic (related donor) HSCT, conditioned with busulfan plus cyclophosphamide, and exposed to GVHD prophylaxis with cyclosporine plus methotrexate.	UDCA 300 mg twice daily (or 300 mg + 600 mg if body weight was > 90 kg) compared with placebo.	Placebo	Seattle	(19)
	AlloHSCT AutoHSCT	56 patients submitted to AlloSCT (related donor or unrelated/mismatched donor) and 15 to autologous hematopoietic stem cell transplantation were randomized to receive or not primary prophylaxis with UDCA.	UDCA 600 mg daily, from day-21 up to day +80	No specific treatment	Seattle	(20)
	AlloHSCT AutoHSCT	81 patients underwent allogeneic HSCT and 88 autologous HSCT.	UDCA 300mg twice daily + heparin 5U/Kg (starting up to 24h before conditioning) up to day +30	Heparin	Modified Seattle	(21)
	AlloHSCT	132 patients receiving allogeneic HSCT from related donors and 110 from matched unrelated donors were randomized to receive primary prophylaxis with UDCA or placebo.	UDCA in the dose of 12 mg/Kg/day from 24 hours before starting the conditioning regimen up to D+90 after transplantation	No specific treatment	Seattle / Baltimore	(22)
Heparin	AlloHSCT AutoHSCT	79 patients undergoing allogeneic HSCT (non-T cell depleted) and 81 undergoing autologous HSCT were randomized to receive or not heparin	Heparin at 100 U/kg/day in continuous infusion from day -8 up to day +30 after HSCT.	No specific treatment	Seattle	(23)
	AutoHSCT	92 patients undergoing autoHSCT (without criteria for high risk of VOD) randomized to receive or not heparin	Heparin at 1 mg/Kg in continuous infusion by day 0 until recovery or discharge	No specific treatment	Seattle	(24)
Fresh frozen plasma	AlloHSCT	43 patients (of whom 15 were children) undergoing alloHSCT and with a high risk of developing VOD (exposed to intensified conditioning regimens, undergoing second SCT, or with previous liver	FFP administered twice weekly and up to day+28 of HSCT according to body weight: 1U (80 ml) if <10 kg; 2U for 10–20 kg, 3U for 20–30 Kg, 4U for 30–40 kg and 5U if >40 Kg.	No specific treatment	Seattle	(25)

		dysfunction) were randomized to receive or not FFP				
brotide	AlloHSCT AutoHSCT	Patients aged <18 years with one or more risk factors for VOD development, undergoing allogeneic or autologous HSCT. Use of UDCA permitted in both groups.	Defibrotide 25 mg/kg/day starting with the conditioning regimen up to day+30 after HSCT.	No specific treatment	Modified Seattle	(26)
	AlloHSCT AutoHSCT	Adult (>16 years) and pediatric patients (<16 years) receiving alloHSCT or autologous HSCT (the former, only pediatric ones) were randomized to receive or not defibrotide if considered with high risk of developing SOS/VOD.	Defibrotide 25 mg/kg/day starting with the conditioning regimen up to day+21 at least and no more than day+30 after HSCT.	No specific treatment	Modified Seattle	(27)
cetyl-L-steine	AlloHSCT	Patients undergoing allogeneic HSCT were randomized to receive or not NAC if risk factors were present (elevated bilirubin, ALT, or AST). 28 patients were exposed to FTBI (9 with NAC prophylaxis) and 48 to BuCy conditioning (20 exposed to NAC).	NAC infusion of 6 hours at a dose of 100 mg/Kg/day until normalization of bilirubin, ALT, and AST values.	No specific treatment	Baltimore	(28)
cyl-L-tamine	AlloHSCT AutoHSCT	Patients undergoing allogeneic HSCT (n=7) or autologous HSCT (n=27). Some patients received warfarin until platelet counts dropped below 50 000/uL (nine in the experimental arm and two in the control)	Daily infusion of 50 g glycyl-L-glutamine	Daily infusion of 50 g of an isonitrogenous mixture of non-essential amino acids	Not specified (without incidence of VOD in both analysed arms)	(29)

Legend: BuCy - busulfan plus cyclophosphamide; FTBI - fractionated total body irradiation; GVHD – graft versus host disease; HSCT -hematopoietic stem cell transplantation; NAC - N-acetyl-L-cysteine; SCT – stem cell transplant.

3.3 Outcomes of different prophylactic interventions

The pooled data of the odds of SOS/VOD in patients undergoing HSCT (either autologous or allogeneic) was analyzed in a pairwise comparison fashion, taking into consideration the direct comparisons and the confidence intervals for the odds traced. Thereafter, direct and indirect comparisons were pooled, and

data summarized in a netrank approach taking into consideration the SUCRA indexes evaluated under a consistency model.

A subgroup analysis including only patients undergoing allogeneic HSCT was performed.

3.3.1 Patients undergoing allogeneic or autologous hematopoietic stem cell transplantation

When considering all patients exposed to cell-based therapies (**figure 2**, n=1795), prophylaxis with fresh frozen plasma was associated with the lowest odds of SOS/VOD development in a pairwise comparison [OR of 0.11; 95% CI: 0.00−2.89]. UDCA exhibited an OR of 0.38 [95% CI: 0.14−1.06] and this result was not significantly different from that obtained for the association of UDCA and heparin, which exhibited an OR of 0.42 [95% CI: 0.05−3.86]. Interestingly, defibrotide displayed only an OR of 0.64 [95% CI: 0.23−1.77]. Although our pairwise comparisons display a moderate heterogeneity (I^2=67.5%), such a finding is expected taking into consideration the standardization of hematopoietic transplantation protocols deployed in patients not infrequently heavily pre-treated and with a wide range of comorbidities that may further influence the incidence of SOS/VOD and even the efficacy of prophylactic protocols.

A network meta-analysis taking into account the five direct comparisons and ten indirect comparator arms allowed the estimation of different primary prophylaxis strategies' efficacy through a cumulative ranking probability index. SUCRA indexes were retrieved and were generally in agreement with the evidence emanated by the pairwise study. UDCA exhibited a SUCRA index of 0.720 (ranking higher in terms of efficacy), while the defibrotide cumulative probability area under the curve was 0.486 (fourth in the ranking). N-acetyl-L-cysteine was associated with the lowest pooled efficacy (SUCRA of 0.442).

3.3.2 Subgroup analysis of patients exposed to allogeneic hematopoietic stem cell transplantation

A pairwise analysis in the subgroup of patients treated with allogeneic hematopoietic stem cell transplantation (**figure 3**) unveiled the lowest (although not statistically significant) odds of SOS/VOD development in the ones prophylactically treated with fresh frozen plasma, OR=0.11 [95% CI: 0.00−3.21]. Although UDCA and defibrotide exhibited similar OR in the former analysis, a marginally higher SUCRA index is achieved by defibrotide (0.650) by comparison with the UDCA (0.639), when considering the network approach operated under a Bayesian framework. N-acetyl-L-cysteine prophylaxis ranked once again in the last position (0.462), herein precluding this approach as a potentially effective prophylactic strategy.

4. Discussion

As an attempt to prevent the development of SOS/VOD, different therapeutic strategies have been tested. Ursodeoxycholic acid (UDCA) was shown to enhance biliary secretion of bile acids and bilirubin

glucuronides through post-transcriptional up-regulation of export pumps. This agent also exerts anti-apoptotic effects in cholestatic hepatocytes (through a decrease in mitochondrial release of cytochrome C) and enhances bicarbonate secretion in cholangiocytes (employing an increase in cytosolic calcium that stimulates chloride/bicarbonate antiporter channel). Interestingly, UDCA displays an immunomodulatory role by decreasing both the expression of MHC (major histocompatibility complex) classes I and II in hepatocytes (the former by a non-selective binding to glucocorticoid receptor that suppresses IFN-γ pathway) (30). Unfractionated heparin, on the other hand, acts by binding and activation of antithrombin that ultimately inactivates factor Xa activity and thrombin, as well as the thrombin-dependent platelet activation and factors V and VIII release (31). Concerning the microvascular prothrombotic status and clot formation in hepatic sinusoids and venules (4), heparin may play a role in primary prophylaxis, yet at the expense of an increased bleeding risk. Defibrotide, in another spectrum, is an orphan-drug, known for its profibrinolytic activities on the dependence of an increased expression and activity of tissue plasminogen activator, tissue factor pathway inhibitor, and thrombomodulin; coupled with its antithrombotic properties on the dependence of the reduced expression of plasminogen activator inhibitor, platelet-activating factor, and thrombin; ultimately decreasing platelet activation and secondary hemostasis. Defibrotide was also shown to downregulate MHC-I and II expression (the former induced by prostaglandins E2 and I2 increased expression) (32). Given its master player role in hemostasis, vascular biology, and immune-modulatory properties, defibrotide has been explored not only in the treatment but also as a prophylactic strategy in patients with a higher risk of developing an SOS/VOD. Lastly, and considering the tested strategies in former trials, N-acetyl-L-cysteine was explored given its role as a scavenger of reactive oxygen species and glutathione precursor (33). To date, there is still no consensus on the demand and efficacy of primary prophylactic strategies in SOS/VOD, as well as the target population that could benefit most from this strategy.

In this analysis, we report an aggregated overview of the role of primary prophylaxis of SOS/VOD in patients undergoing hematopoietic stem cell transplantation. Considering all patients undergoing cell-based therapies, UDCA scored higher. However, when only allotransplanted patients were analyzed, defibrotide marginally outcasted UDCA in this subset of patients. This observation, beyond being related to the nature of the procedure (autologous or allogeneic), potentially reflects patient and disease intrinsic characteristics, that vary across those two therapeutic procedures. Allotransplanted patients are typically diagnosed with more aggressive neoplasms (acute leukemias, for example) (34); and during induction and consolidation therapies are exposed to significant cumulative doses of cytotoxic agents, exhibiting a higher need for blood transfusions that otherwise induce hemosiderosis and increase iron deposits in liver (35). The conditioning regimens vary widely across studies (and even over time), being well known that, for example, liver irradiation may potentiate SOS/VOD incidence as shown in a previous analysis where the incidence of this complication was increased in patients exposed to single-dose versus hyperfractioned regimens (36). In our analysis, the distribution of allotransplanted patients whose conditioning regimens were dependent upon total body radiation was not uniformly distributed across different trials (neither the pre-transplantation needs for irradiation of the abdominal compartment), and this circumstance may impose a milder heterogeneity in the findings. Immune reconstitution following

allogeneic transplantation of hematopoietic progenitors will also induce cellular damage, depending on the degree of HLA (human leukocyte antigen) matching (37), another observation that may impose an undetermined heterogeneity in the pooled population.

In light of the current knowledge, it is fair to hypothesize that the minimal advantage of primary prophylaxis with defibrotide in allotransplanted patients may arise from its immunomodulatory and iron chelation properties (32) that secondarily reduce oxidative stress and inflammation associated with the iron-induced liver disease. In fact, elevated serum ferritin levels before hematopoietic stem cell transplantation are regarded as an important risk factor for SOS/VOD development (38). Pre-transplantation transfusion dependency (associated with hemosiderosis) was associated with lower overall survivals, a higher burden of graft-versus-host disease, and an increased non-relapse mortality in patients undergoing myeloablative conditioning regimens (39); with therapeutic strategies to deplete iron stores in historical cohorts even showing an increase in liver function tests of patients after bone marrow transplantation (40).

Beyond the patient, disease, and therapeutic measures intrinsic properties that may influence the hazard of SOS/VOD development, observational bias in clinical trials may also limit the extrapolation of general conclusions emanated from them. For instance, recent trials were pivotal by showing that there was a disagreement in SOS/VOD diagnosis between local physicians (thoroughly accompanying the patient journey) and the ones responsible for centrally and blindly revising clinical and analytical data (27). The dependence of the diagnosis of this entity on clinical and analytical criteria (both dynamic) may undoubtedly influence its diagnosis and reported incidence.

Overall, when considering the pharmacological agents assessed in our analysis, ursodeoxycholic acid, beyond highly affordable, displays a pleiotropic pharmacological action, modulating both liver bile acids secretion, hepatocyte resistance to apoptosis and decreasing the potential for immune-mediated injury by downregulating MHC expression in liver cells surface (30). For these reasons, evidence prompts its use as a beneficial prophylactic strategy in patients undergoing hematopoietic stem cell transplantation.

When considering only patients undergoing allogeneic bone marrow transplantation, we systematize and report, for the first time, an aggregated overview of the primary prophylactic strategies for SOS/VOD. Despite the population heterogeneity that cannot be avoided in the pooled analysis, taking into consideration our findings, the pharmacological principles of the different therapeutic strategies, and the immune (dis)regulation associated with each particular transplant, we open doors to a more rationale critical thinking and decision making in the clinical practice, by proposing a hierarchization of therapeutic strategies.

Conclusion

The adoption of primary prophylactic regimens for SOS/VOD in patients undergoing hematopoietic stem cell transplantation remains a controversial issue. The diversity of pathologies imposing the need for a cell-based therapy, co-joined with the heterogeneity of conditioning regimens and patients' basal

immunological fitness and immune reconstitution after stem cell engraftment impose mild limitations in the generalization of observations coming from clinical trials.

Our network meta-analysis revealed that UDCA is an overall promising strategy, considering both patients undergoing autologous or allogeneic hematopoietic stem cell transplantation. A subgroup analysis in allotransplanted patients (made whenever specific data about this group was available and retrievable from clinical trials) also prompted defibrotide as a promising strategy in this setting. It is expected that some patients (we hypothesize the ones with liver iron overload as some of them, for example) may benefit from defibrotide instead of UDCA. Notwithstanding, due to its accessibility and affordability, UDCA insurges as the potentially more promising baseline strategy. Further studies are warranted to identify the patients who benefit more from primary prophylaxis, as well as to systematize the clinical and biological markers that indicate the need for a specific therapeutic approach.

Declarations

The research study adhered to the Cochrane collaboration guidelines for systematic reviews.

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References

1.   Carreras E, Bertz H, Arcese W, Vernant J-P, Tomás J-F, Hagglund H, et al. Incidence and Outcome of Hepatic Veno-Occlusive Disease After Blood or Marrow Transplantation: A Prospective Cohort Study of the European Group for Blood and Marrow Transplantation. Blood [Internet]. 1998 Nov 15;92(10):3599–604.

2.   Barker CC, Butzner JD, Anderson RA, Brant R, Sauve RS. Incidence, survival and risk factors for the development of veno-occlusive disease in pediatric hematopoietic stem cell transplant recipients. Bone Marrow Transplant. 2003 Jul;32(1):79–87.

3.   Carreras E, Diaz-Ricart M. The role of the endothelium in the short-term complications of hematopoietic SCT. Bone Marrow Transplant. 2011 Dec;46(12):1495–502.

4.   Richardson PG, Ho VT, Cutler C, Glotzbecker B, Antin JH, Soiffer R. Hepatic Veno-Occlusive Disease after Hematopoietic Stem Cell Transplantation: Novel Insights to Pathogenesis, Current Status of Treatment, and Future Directions. Biol Blood Marrow Transplant [Internet]. 2013;19(1, Supplement):S88–90.

5.   Bonifazi F, Barbato F, Ravaioli F, Sessa M, Defrancesco I, Arpinati M, et al. Diagnosis and Treatment of VOD/SOS After Allogeneic Hematopoietic Stem Cell Transplantation. Front Immunol. 2020;11:489.

6.   Mohty M, Malard F, Abecassis M, Aerts E, Alaskar AS, Aljurf M, et al. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives-a position statement from the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant. 2015 Jun;50(6):781–9.

7.   Rajvanshi P, Shulman HM, Sievers EL, McDonald GB. Hepatic sinusoidal obstruction after gemtuzumab ozogamicin (Mylotarg) therapy. Blood. 2002 Apr;99(7):2310–4.

8.   Ladha A, Mannis G, Muffly L. Hepatic veno-occlusive disease in allogeneic stem cell transplant recipients with prior exposure to gemtuzumab ozogamicin or inotuzumab ozogamicin. Leuk Lymphoma. 2021 Feb;62(2):257–63.

9.   Peres E, Kintzel P, Dansey R, Baynes R, Abidi M, Klein J, et al. Early intervention with antithrombin III therapy to prevent progression of hepatic venooclusive disease. Blood Coagul fibrinolysis an Int J Haemost Thromb. 2008 Apr;19(3):203–7.

10.   Pabinger I, Thaler J. How I treat patients with hereditary antithrombin deficiency. Blood. 2019 Dec;134(26):2346–53.

11.   Seifert C, Wittig S, Arndt C, Gruhn B. Heparanase polymorphisms: influence on incidence of hepatic sinusoidal obstruction syndrome in children undergoing allogeneic hematopoietic stem cell transplantation. J Cancer Res Clin Oncol. 2015 May;141(5):877–85.

12.   McDonald GB, Sharma P, Matthews DE, Shulman HM, Thomas ED. Venocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence, and predisposing factors. Hepatology. 1984;4(1):116–22.

13.   Jones RJ, Lee KS, Beschorner WE, Vogel VG, Grochow LB, Braine HG, et al. Venooclusive disease of the liver following bone marrow transplantation. Transplantation. 1987 Dec;44(6):778–83.

14.   Mohty M, Malard F, Abecassis M, Aerts E, Alaskar AS, Aljurf M, et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation. Bone Marrow Transplant. 2016 Jul;51(7):906–12.

15.   Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.4 (updated August 2023). Cochrane, 2023.

16.   Mbuagbaw L, Rochwerg B, Jaeschke R, Heels-Andsell D, Alhazzani W, Thabane L, et al. Approaches to interpreting and choosing the best treatments in network meta-analyses. Vol. 6, Systematic reviews. England; 2017. p. 79.

17.   Balduzzi S, Rücker G, Nikolakopoulou A, Papakonstantinou T, Salanti G, Efthimiou O, et al. netmeta: An R Package for Network Meta-Analysis Using Frequentist Methods. J Stat Softw [Internet]. 2023 Mar 23;106(2 SE-Articles):1–40.

18.   van Valkenhoef G, Dias S, Ades AE, Welton NJ. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. Res Synth Methods. 2016 Mar;7(1):80–93.

19.   Essell JH, Schroeder MT, Harman GS, Halvorson R, Lew V, Call, et al. Ursodiol prophylaxis against hepatic complications of allogeneic bone marrow transplantation - A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1998;128(12):975-+.

20.   Ohashi K, Tanabe J, Watanabe R, Tanaka T, Sakamaki H, Maruta A, et al. The Japanese multicenter open randomized trial of ursodeoxycholic acid   prophylaxis for hepatic veno-occlusive disease after stem cell   transplantation. Am J Hematol. 2000;64(1):32–8.

21.   Park SH, Lee MH, Lee H, Kim HS, Kim K, Kim WS, et al. A randomized trial of heparin plus ursodiol vs heparin alone to prevent hepatic veno-occlusive disease after hematopoietic stem cell transplantation. Bone Marrow Transplant. 2002;29(2):137–43.

22.   Ruutu T, Eriksson B, Remes K, Juvonen E, Volin L, Remberger M, et al. Ursodeoxycholic acid for the prevention of hepatic complications in allogeneic stem cell transplantation. [Internet]. Vol. 100, Blood. United States; 2002. p. 1977–83.

23.   Attal M, Huguet F, Rubie H, Huynh A, Charlet J-P, Payen J-L, et al. Prevention of hepatic veno-occlusive disease after bone marrow transplantation by continuous infusion of low-dose heparin: A prospective, randomized trial. Blood [Internet]. 1992;79(11):2834–40.

24.   Marsa-Vila L, NC G, JP L, Labopin M, MC D-M, Fouillard L, et al. Prophylactic heparin does not prevent liver veno-occlusive disease following autologous bone marrow transplantation. [Internet]. Vol. 47, European journal of haematology. England; 1991. p. 346–54.

25.   Matsumoto M, Kawa K, Uemura M, Kato S, Ishizashi H, Isonishi A, et al. Prophylactic fresh frozen plasma may prevent development of hepatic VOD after stem cell transplantation via ADAMTS13-mediated restoration of von Willebrand factor plasma levels. Bone Marrow Transplant. 2007;40(3):251–9.

26.   Corbacioglu S, Cesaro S, Faraci M, Valteau-Couanet D, Gruhn B, Rovelli A, et al. Defibrotide for prophylaxis of hepatic veno-occlusive disease in paediatric haemopoietic stem-cell transplantation: an open-label, phase 3, randomised controlled trial. Lancet. 2012;379(9823):1301–9.

27.   Grupp SA, Corbacioglu S, Kang HJ, Teshima T, Khaw SL, Locatelli F, et al. Defibrotide plus best standard of care compared with best standard of   care alone for the prevention of sinusoidal obstruction syndrome (HARMONY): a randomised, multicentre, phase 3 trial. LANCET Haematol. 2023;10(5):E333–45.

28.   Barkholt L, Remberger M, Hassan Z, Fransson K, Omazic B, BM S, et al. A prospective randomized study using N-acetyl-L-cysteine for early liver toxicity after allogeneic hematopoietic stem cell transplantation. [Internet]. Vol. 41, Bone marrow transplantation. England; 2008. p. 785–90.

29.   SA B, Goringe A, Fegan C, SV D, Giddings J, JA W, et al. Parenteral glutamine protects hepatic function during bone marrow transplantation. [Internet]. Vol. 22, Bone marrow transplantation. England; 1998. p. 281–4.

30.   Beuers U. Drug insight: Mechanisms and sites of action of ursodeoxycholic acid in cholestasis. Nat Clin Pract Gastroenterol Hepatol. 2006 Jun;3(6):318–28.

31.   Hirsh J, Anand SS, Halperin JL, Fuster V. Mechanism of action and pharmacology of unfractionated heparin. Vol. 21, Arteriosclerosis, thrombosis, and vascular biology. United States; 2001. p. 1094–6.

32.   Pescador R, Capuzzi L, Mantovani M, Fulgenzi A, Ferrero ME. Defibrotide: properties and clinical use of an old/new drug. Vascul Pharmacol. 2013;59(1–2):1–10.

33.   Pedre B, Barayeu U, Ezeriņa D, Dick TP. The mechanism of action of N-acetylcysteine (NAC): The emerging role of H(2)S and sulfane sulfur species. Pharmacol Ther. 2021 Dec;228:107916.

34.   Snowden JA, Sánchez-Ortega I, Corbacioglu S, Basak GW, Chabannon C, de la Camara R, et al. Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2022. Bone Marrow Transplant. 2022 Aug;57(8):1217–39.

35.   Shander A, Cappellini MD, Goodnough LT. Iron overload and toxicity: the hidden risk of multiple blood transfusions. Vox Sang. 2009 Oct;97(3):185–97.

36.   Girinsky T, Benhamou E, Bourhis JH, Dhermain F, Guillot-Valls D, Ganansia V, et al. Prospective randomized comparison of single-dose versus hyperfractionated total-body irradiation in patients with hematologic malignancies. J Clin Oncol Off J Am Soc Clin Oncol. 2000 Mar;18(5):981–6.

37.   Xia Y, Qin H, Yang J. Hepatic veno-occlusive disease development in the hematopoietic stem cell transplantation patients: incidence and associated risk factors, a meta-analysis. Eur J Gastroenterol Hepatol. 2021 Jun;33(6):872–84.

38.   Morado M, Ojeda E, Garcia-Bustos J, Aguado MJ, Arrieta R, Quevedo E, et al. BMT: Serum Ferritin as Risk Factor for Veno-occlusive Disease of the Liver. Prospective Cohort Study. Hematology. 2000;4(6):505–12.

39.   Alessandrino EP, Della Porta MG, Bacigalupo A, Malcovati L, Angelucci E, Van Lint MT, et al. Prognostic impact of pre-transplantation transfusion history and secondary iron overload in patients with myelodysplastic syndrome undergoing allogeneic stem cell transplantation: a GITMO study. Haematologica. 2010 Mar;95(3):476–84.

40.   McKay PJ, Murphy JA, Cameron S, Burnett AK, Campbell M, Tansey P, et al. Iron overload and liver dysfunction after allogeneic or autologous bone marrow transplantation. Bone Marrow Transplant. 1996 Jan;17(1):63–6.
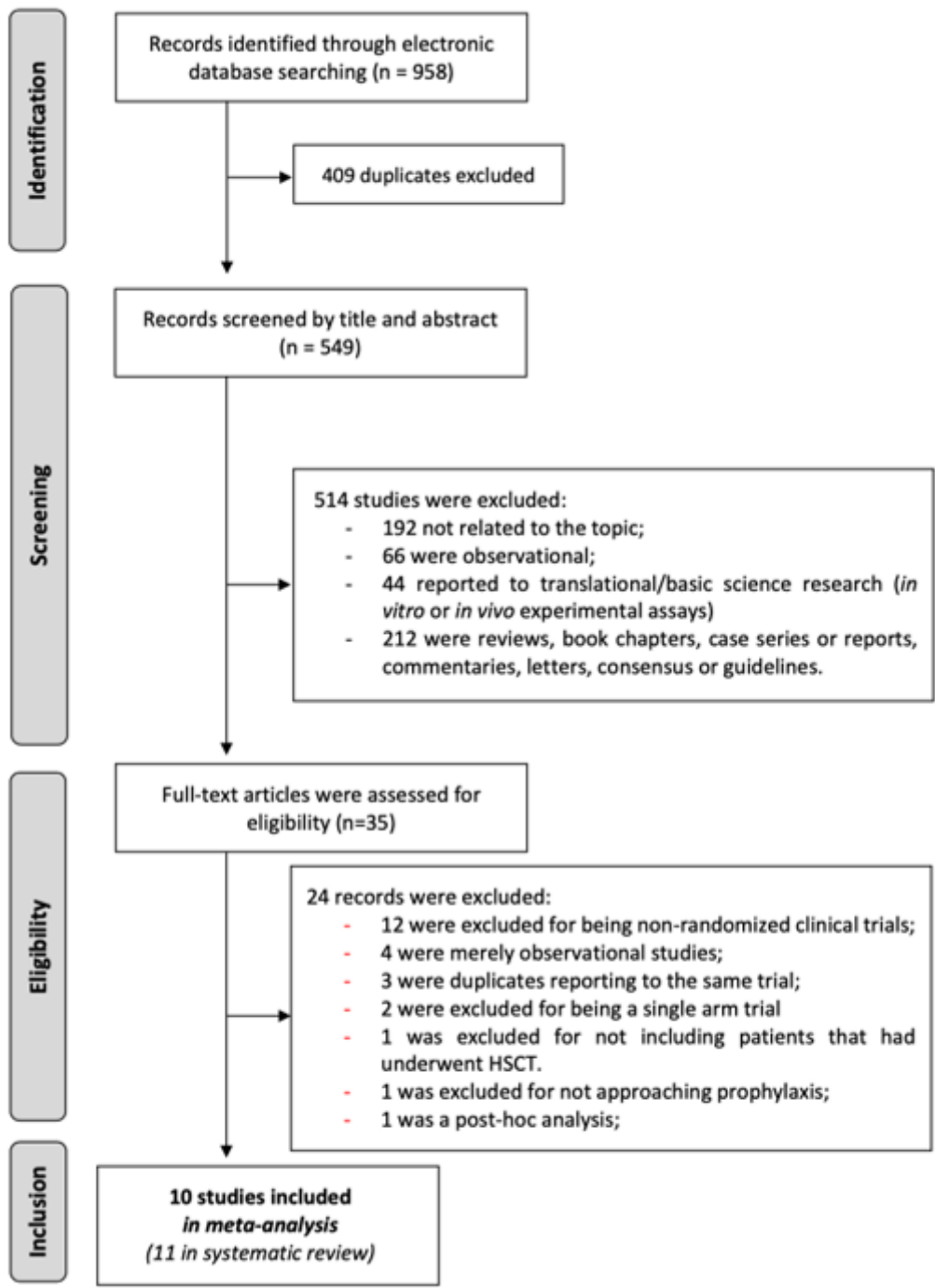
Figures

Figure 1

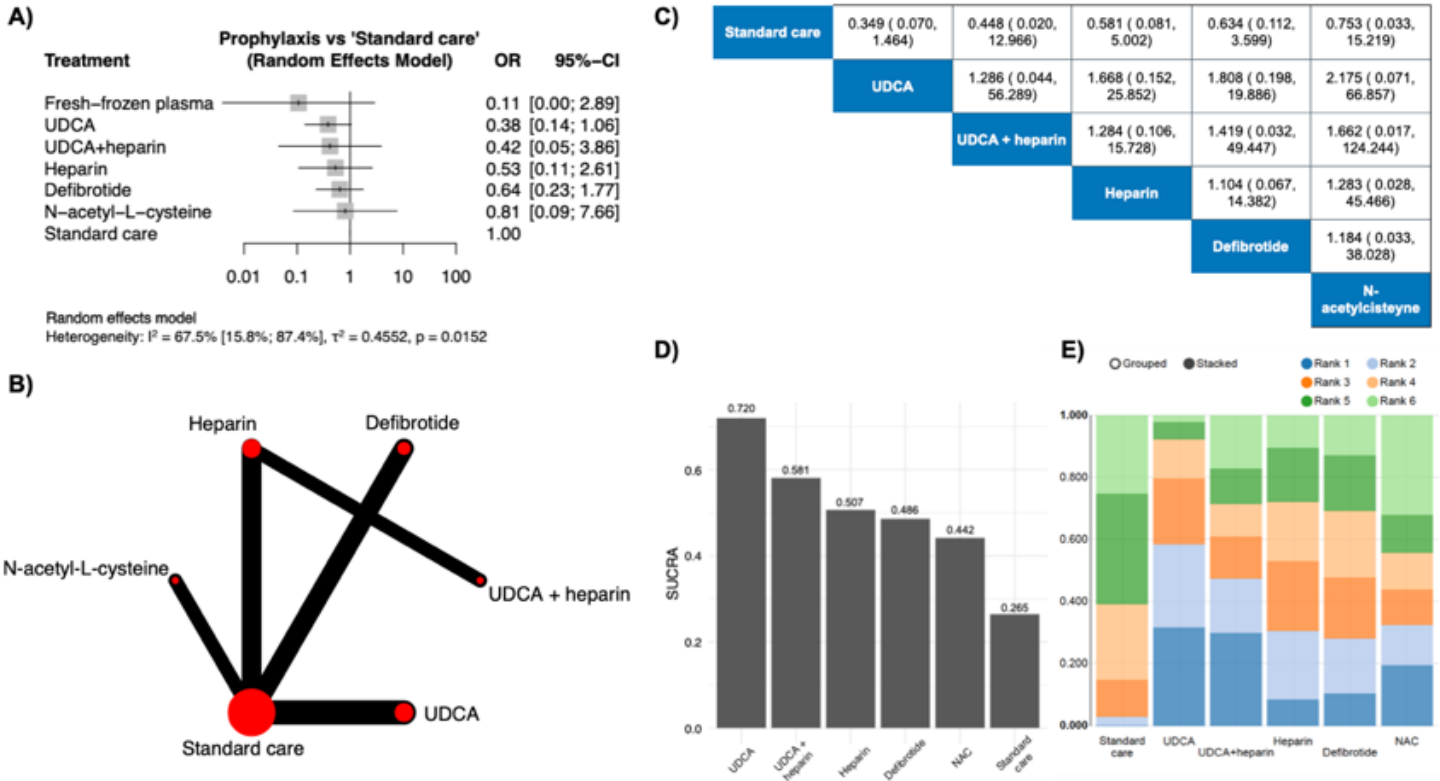Flowchart of data selection.

Figure 2

Pooled analysis including all patients undergoing HSCT and enrolled in a clinical trial exploring the efficacy of a prophylactic regimen for SOS/VOD. A - pairwise meta-analysis addressing the direct comparisons included in the evidence; B - network analyzed under a consistency model; C − odds ratio of included interventions and 95% CI (effect of the column-defining intervention relative to the row-defining intervention); D − SUCRA plots; E - *rankogram* of prophylactic strategies.
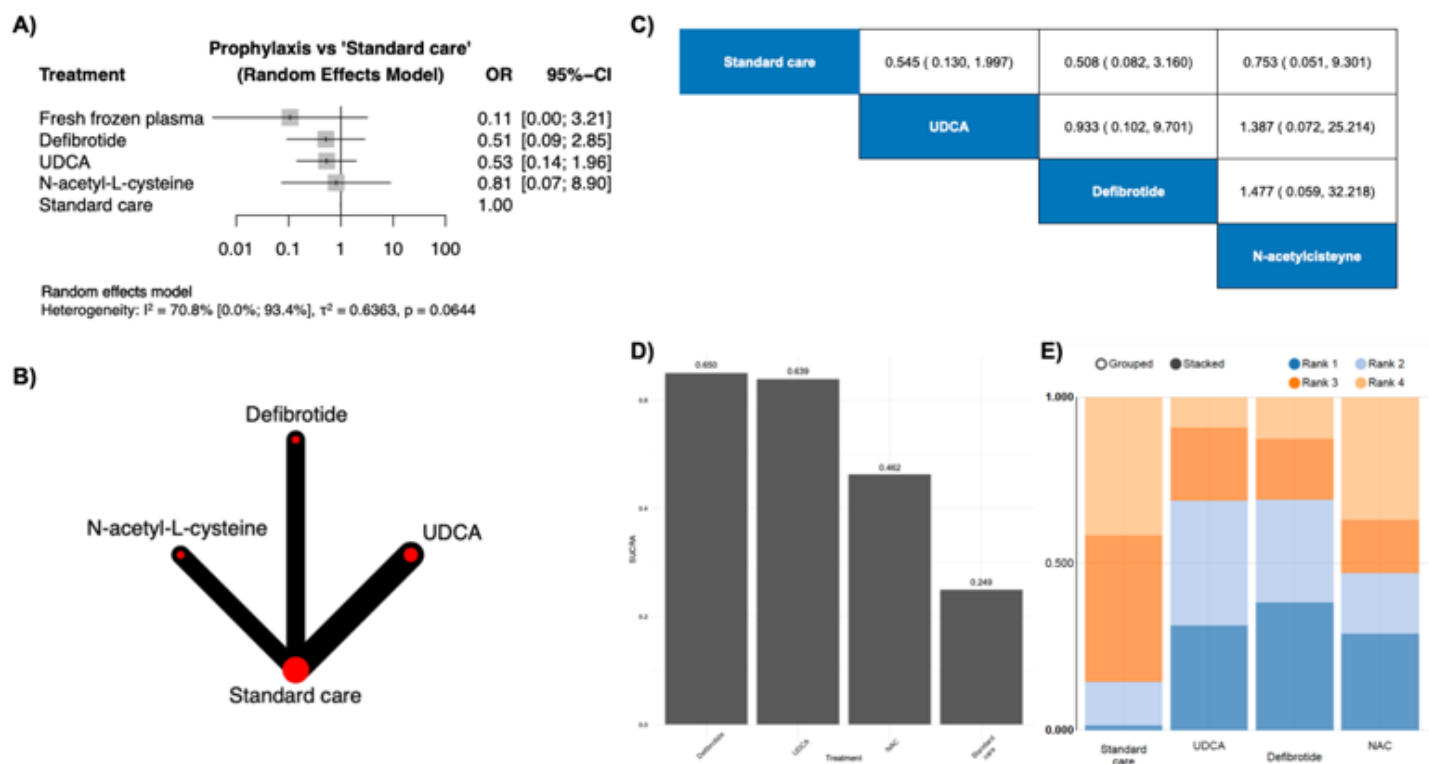
Figure 3

Pooled subgroup analysis including only patients undergoing allogeneic HSCT (both related and unrelated donors included) and enrolled in a randomized trial exploring the efficacy of a prophylactic regimen for SOS/VOD. A - pairwise meta-analysis addressing the direct comparisons included in the evidence; B - network analyzed under a consistency model; C – odds ratio of included interventions and 95% CI (effect of the column-defining intervention relative to the row-defining intervention); D – SUCRA plots; E - *rankogram* of prophylactic strategies.

Supplementary Files

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