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Revisión Sistemática

The effectiveness of Thromboelastography (TEG) or thromboelastometry (ROTEM) to guide transfusion treatment versus usual care in liver transplant.
A eficácia da tromboelastografia (TEG) ou tromboelastometria (ROTEM) para orientar o tratamento transfusional versus o tratamento usual no transplante de fígado.
La eficacia de la tromboelastografía (TEG) o tromboelastometría (ROTEM) para guiar el tratamiento de transfusión versus la atención habitual en el trasplante de hígado.

Rando K[1]

[1]Director of the Anesthesiology Services, Hospital Central de las Fuerzas Armadas (H.C.FF.AA.), Liver Transplantation Unit. Contacto: arando@dns.hcffaa.gub.uy, karina.rando@gmail.com

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ABSTRACT

The accuracy of the TEG/ROTEM as diagnostic test has been proved[(19)] and systematic reviews were performed to aggregate the evidence from different clinical scenarios (mainly cardiac surgery). Assess the impact of the intraoperative point of care use of TEG or ROTEM versus conventional coagulation tests (CCT) on the blood components transfusion, bleeding, complications, mortality, hospitalization and costs during adult LTX surgeries. I used PICOS framework to establish the research questions (objectives section) and the inclusion criteria. Type of studies included. The eligibility criteria were randomized controlled trials and non-randomized controlled trials (RCTs and non-RCTs).

Primary outcomes: mortality at maximal follow up, allogeneic transfusion requirements: packaged red cells (PRC), platelets, fresh frozen plasma(FFP), cryoprecipitates), complications (medical adverse event that may be related to the coagulation status). Secondary outcomes: blood loss (however

measured by authors), total hospital stays, intensive care unit (ICU) stay, costs (of the transplant surgery or of the patient in-hospital treatment). A total of 183 studies were identified and a PRISMA-based diagram was constructed and 8 of them were selected to assess. Six articles were found in full text and were screened for inclusion and exclusion criteria. Five trials had the selected outcomes and inclusion criteria and the quality was assessed with a critical appraisal approach to identify bias and confounders. In conclusion, TEG/ROTEM directed blood products replacement in LTX might be effective in reducing FFP transfusion during the intraoperative. Further studies are required to confirm this finding and to assess the overall requirements of other blood products, bleeding mortality and complications.
Key words: TEG, ROTEM, liver transplantation.

RESUMEN

La precisión del TEG / ROTEM como prueba de diagnóstico se ha demostrado [19] y se realizaron revisiones sistemáticas para agregar la evidencia de diferentes escenarios clínicos (principalmente cirugía cardíaca). Evaluar el impacto del uso de TEG o ROTEM en el punto de atención intraoperatoria versus las pruebas de coagulación (CCT) convencionales en la transfusión de componentes sanguíneos, sangrado, complicaciones, mortalidad, hospitalización y costos durante las cirugías de LTX en adultos. Utilicé el marco PICOS para establecer las preguntas de investigación (sección de objetivos) y los criterios de inclusión. Tipo de estudios incluidos. Los criterios de elegibilidad fueron los ensayos controlados aleatorios y los ensayos controlados no aleatorios (ECA y no controlados).

Resultados primarios: mortalidad en el seguimiento máximo, requisitos de transfusión alogénica: glóbulos rojos envasados (PRC), plaquetas, plasma fresco congelado (FFP), crioprecipitados, complicaciones (evento adverso médico que puede estar relacionado con el estado de coagulación). Resultados secundarios: pérdida de sangre (sin embargo, medida por los autores), estadías totales en el hospital, estadía en la unidad de cuidados intensivos (UCI), costos (de la cirugía de trasplante o del tratamiento hospitalario del paciente). Se identificaron un total de 183 estudios y se construyó un diagrama basado en PRISMA y se seleccionaron 8 de ellos para evaluar. Se encontraron seis artículos en texto completo y se examinaron para criterios de inclusión y exclusión. Cinco ensayos tuvieron los resultados seleccionados y los criterios de inclusión, y la calidad se evaluó con un enfoque de evaluación crítica para identificar sesgos y factores de confusión. En conclusión, el reemplazo de productos sanguíneos dirigidos por TEG / ROTEM en LTX podría ser eficaz para reducir

la transfusión de FFP durante el tratamiento intraoperatorio. Se requieren estudios adicionales para confirmar este hallazgo y evaluar los requisitos generales de otros productos sanguíneos, la mortalidad por sangrado y las complicaciones.
Palabras clave: TEG, ROTEM, trasplante hepático.

RESUMO

A precisão do TEG / ROTEM como teste diagnóstico tem sido comprovada [19] e revisões sistemáticas foram realizadas para agregar as evidências de diferentes cenários clínicos (principalmente cirurgia cardíaca). Avaliar o impacto do uso de TEG ou ROTEM no ponto intraoperatório versus testes convencionais de coagulação (TCC) na transfusão de hemocomponentes, sangramento, complicações, mortalidade, hospitalização e custos durante cirurgias de LTX em adultos. Eu usei o framework PICOS para estabelecer as questões de pesquisa (seção de objetivos) e os critérios de inclusão. Tipo de estudos incluídos. Os critérios de elegibilidade foram ensaios clínicos randomizados e não-randomizados controlados (ECRs e não-ECR).
Desfechos primários: mortalidade no seguimento máximo, necessidade de transfusão alogênica: eritrócitos empacotados (PRC), plaquetas, plasma fresco congelado (FFP), crioprecipitados), complicações (evento adverso médico que pode estar relacionado ao estado de coagulação).
Desfechos secundários: perda de sangue (porém medida pelos autores), internação total, internação em unidade de terapia intensiva (UTI), custos (da cirurgia de transplante ou do tratamento intra-hospitalar do paciente). Um total de 183 estudos foram identificados e um diagrama baseado no PRISMA foi construído e 8 deles foram selecionados para avaliação. Seis artigos foram encontrados em texto completo e foram selecionados para inclusão e critérios de exclusão. Cinco ensaios tiveram os resultados selecionados e critérios de inclusão e a qualidade foi avaliada com uma abordagem de avaliação crítica para identificar vieses e fatores de confusão. Em conclusão, o TEG / ROTEM direcionado à reposição de hemoderivados no LTX pode ser eficaz na redução da transfusão de PFC durante o intraoperatório. Mais estudos são necessários para confirmar este achado e para avaliar os requisitos gerais de outros produtos sangüíneos, sangramento da mortalidade e complicações.
Palavras-chave: TEG, ROTEM, transplante de fígado.

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Aceptado: 3/10/18

Background

Description of liver transplant (LTX) surgery and the intervention

Patients who are candidates for LTX usually present a tendency to bleed but occasionally they might have thrombosis due to the presence of portal hypertension and the deficit in metabolism of factors that lyse the clot. During the LTX, other changes, such as loss of coagulation factors, platelet consumption, heparin-simile phenomena, alter the previous balance, and severe coagulation disorders are common. Conventional coagulation tests are not precise and coagulation monitoring deserves special attention in TLX [1, 2, 3].

Thromboelastography (TEG) and thromboelastometry (ROTEM) can be use as "point of care" tests (POC) allowing immediate therapeutic decisions [4]. The objective of using TEG/ROTEM protocols do guide blood product replacement in LTX is to anticipate to coagulation disorders, avoiding situations that lead to massive indiscriminate transfusions [5]. TEG/ROTEM discriminate which stage of coagulation is altered, so, the appropriate blood product can be transfused [6, 7]. The reduction of complications related to transfusions, as well as the reduction of the volume of transfused blood components could reduce the costs of surgery[8].

Another advantage of TEG/ROTEM is that is the only coagulation monitor or test that can diagnose hypercoagulability disorders, which can be presented in LTX and may easily lead to life threating conditions[9].

Background and Importance of this revision

In 2011 TEG/ROTEM could not be recommended for LYX due to the lack of evidence of benefits in outcomes [10]. Despite this, the use of TEG/ROTEM has expanded and new clinical studies have emerged [11, 12, 13, 14, 15, 16, 17, 18]. The recommendations we made in 2011 need to be update.

The accuracy of the TEG/ROTEM as diagnostic test has been proved[19] and systematic reviews were performed to aggregate the evidence from different clinical scenarios (mainly cardiac surgery) [19, 20, 21, 22]. A Cochrane systematic review, analysed measures to reduce bleeding in LTX, even though it was focused on pharmacologic treatment, the authors suggested that TEG may be beneficial in reducing blood loss and transfusions [23].

Objetive

Assess the impact of the intraoperative point of care use of TEG or ROTEM versus conventional coagulation tests (CCT) on the blood components transfusion, bleeding, complications, mortality, hospitalization and costs during adult LTX surgeries.

Methodology

I define the research question and design study as suggested by Carl Counsell in 1997 [24]. Even if the data aimed to collect are quantitative, I am not willing to statistically analyse the data to perform a meta-analysis due to time limitations.

Criteria to consider studies for this review

I used PICOS framework to establish the research questions (objectives section) and the inclusion criteria[25].

Type of studies included. The eligibility criteria were randomized controlled trials and non-randomized controlled trials (RCTs and non-RCTs). The rationale for the inclusion criteria was based on the difficulty of performing a randomization in the context of LTX surgery. The usefulness of TEG/ROTEM was demonstrated in different scenarios; therefore, if a patient has a life-threatening bleeding (which is common in LT), it wouldn't be ethical to deny the TEG/ROTEM because he/she is assigned to the control group of an RCT.

The trials were included irrespective of blinding or sample size. We will limit this study trials with data collected prospectively, regardless of whether the analysis was done prospectively or retrospectively. Cohort study(CS), case-control studies and other non-randomized comparative trials are included.

Exclusions criteria. Trials where: the comparative group didn't match with the intervention group, the main outcomes are limited to the postoperative period, doesn't follow TEG/ROTEM guided algorithm or were not written in English, Spanish, Portuguese, French or Italian.

Types of participants.

Patients undergoing LTX irrespective of age, donor (living or cadaveric) and all reasons for transplantation.

Types of interventions.

The following comparisons will be included:

1-Utilization of intraoperative TEG to diagnose coagulation disorders and guide blood product and fluid replacements versus conventional laboratory blood tests[1] .

2- Utilization of intraoperative ROTEM to diagnose coagulation disorders and guide blood product and fluid replacements versus conventional laboratory blood tests.

Types of outcomes measures

Primary outcomes:

- Mortality at maximal follow up.
- Allogeneic transfusion requirements: packaged red cells (PRC), platelets, fresh frozen plasma(FFP), cryoprecipitates)
- Complications (medical adverse event that may be related to the coagulation status).

Secondary outcomes:

- Blood loss (however measured by authors).
- Total hospital stays.
- Intensive care unit (ICU) stay.
- Costs (of the transplant surgery or of the patient in-hospital treatment).

[1] Conventional laboratory blood tests: fibrinogen, prothrombin time, activated partial thromboplastin time, platelet count.

Search method for studies identification

An electronic search was done (limited to human subjects, without limit of time) in five databases: The Cochrane Central Register of Controlled Trials, Ovid-MEDLINE, LILACS, Global Health (February 24^{t-}2018) and The National Library of Medicine (PubMed) (April 6th-2018). We used a search strategy combining Medical Subject Headings and keywords and synonymous related to the following areas:

1-Intervention: *TEG or ROTEM*

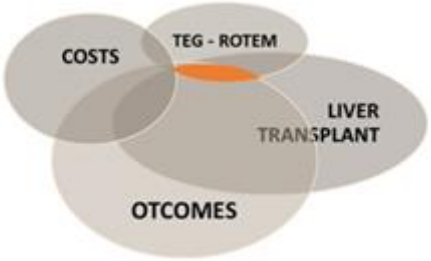
2-Setting: Liver transplantation.

3-Outcomes: mortality, transfusion, complications, blood loss, hospitalization.

4-Costs.

Synonymous, truncation and wildcards were used. **Appendix 1** (A,B,C,D,E). The topics were combined as represented in the diagram of **Figure 1**. The strategy used in each database is detailed in the **Appendix 1**.

Figure 1: Diagram of 4 main areas searched in this review.



The trials selected were those that merge either the four circles or those that merge: liver transplant & TEG/ROTEM with either outcomes or costs.

Data collection and analysis

Selection of the studies

A total of 183 studies were identified and a PRISMA-based diagram was constructed [26] as shown in **Appendix 2**. We screened the titles and abstracts to identify eligible studies and 8 of them were selected to assess, **Appendix 3**.

Six of the 8 relevant articles were found in full text and were screened for inclusion and exclusion criteria. A study was excluded because the protocol that TEG/ROTEM protocol was not used to guide fluid replacement but to guide an intermediate pharmacological action: use of antifibrinolytic drugs[27]. Five trials had the selected outcomes and inclusion criteria and the quality was assessed with a critical appraisal approach to identify bias and confounders [16, 17, 18, 28, 29]. **Appendix 4** (A,B,C,D,E).

We didn't define a quality threshold for inclusion criteria because we choose to give up some rigour in favour of the usefulness of this study. The critical quality appraisal was structured in 5 risk domains, and the weigh given to each one depended on the nature of our studied intervention. The "intervention", "data collection" and "data analysis" domains were considered more important than "allocation and blinding" or "sampling and recruitment". **Appendix 4**.

Appraising quality

Internal methodological quality.

We use the CASP form[2] for the 6 relevant trials and grouped the findings to assess validity of the studies, validity of the results and applicability. **Table 1**. After discarding the study that had no aimed outcomes [(27)], 5 studies were assessed for confounders and bias. After the quality appraisal, one article was excluded due to high risk of bias [(17)]. Another study had a control group that was not the target of our study[(29)], even though, we consider that it is relevant for the interpretation of the results. Three included studies had good study validity and applicability. The differences in results will be discussed.

[2] Critical Appraisal Programme (RCT checklist 13.03.17)

Table 1: Summary of the Quality assessment of the studies included for full text assessment. Data collected with an adapted CASP form for trials

Data collection

GENERAL	VALIDITY OF THE TRIAL				VALIDITY OF THE RESULTS		APPLICABILITY
Autor Journal year	**Clearly focused issue**	**Nº patients entered the trial = considered for conclusions**	**Similarity of the groups previously to the transplant**	**Anaesthesia and surgery protocolization, similarity of treatment between groups.**	**How large was the treatment effect for the aim of this study? (*)**	**How precise was the estimate of the treatment effect? (***)**	**Results are important and applicable in other contexts in LTX (Yes/May be /No)**
Wang SC Transplant Proc. 2010	*Yes*	*24 patients. Unknown for each outcome.*	*Yes, in the variables studied.*	Yes.	⊕⊕⊕◯	⊕◯◯	Yes
Roullet S Liver Transpl. 2015	Yes	60 patients. All were full analysed.	*Yes*	Yes	⊕⊕◯◯	⊕⊕⊕	Yes
Smart L Ann Hepatol. 2017	Yes	68 patients. Unknown for each outcome.	*YES*	YES (**)	⊕⊕⊕⊕	⊕⊕⊕	Yes
De Pietri L Transplant Direct. 2015	Yes	386 patients. 373 were full analysed.	Yes (except MELD)	Yes	⊕⊕⊕⊕	⊕⊕⊕	Results are applicable, but comparison is TEG vs FF-TEG
Alamo JM Transplant Proc. 2013	Yes	303 patients. Unknown for each outcome.	Unknown. Confounders were not assessed	Unknown	⊕⊕⊕◯	⊕◯◯	Yes.
Trzebicki J Ann Transplant 2010	Yes	78 patients. All were full analysed.	Yes	Yes	Unknow due to an intermediate confounder.	Unknow due to an intermediate confounder.	Yes

Type studies: Near RCT or non-RCT with an intervention group (TEG/ROTEM directed therapy) and a retrospective control group. None of the trials were blinded. Those studies shadow with grey were discarded. The light-blue shadowed study was only included for qualitative discussion.

(*) Definitions: How large was the treatment effect?

⊕⊕⊕⊕ **High** = the effect of the intervention was very likely to be effective in at least one of the main outcomes and one secondary outcome.
⊕⊕⊕◯ **Moderate** = the effect of the intervention was likely to be effective in at least one of the main outcomes or very likely to be effective in one of the secondary outcomes.
⊕⊕◯◯ **Low** = the effect of the intervention was not likely to be effective any of the main outcomes or very likely but was likely to be effective in some of the secondary outcomes.
⊕◯◯◯ **No effect** = the effect of the intervention could not be demonstrated in any of the outcomes.

(**) Except for the use of aminocaproic acid and aprotinin that was not known in the control group.

(***) Definitions: How precise was the estimate of the treatment effect (related to the outcomes described)?

⊕⊕⊕ **High precision** = confidence intervals (CI) calculated, and the intervention is likely to affect the outcomes.
⊕⊕◯ **Moderate** = confidence intervals (CI) calculated, and it could not demonstrate that the intervention affects the outcomes.
⊕◯◯ **Low** = There is not CI calculated.

The author extracts the data using a modified EPOC[3] worksheets [30]. **Appendix 5** (A,B,C,D,E). We didn't perform subgroup analysis because there are few studies and are relatively homogeneous: adult patients and setting.

Bias and confounders of individual studies.

We look for possible confounders and bias from the worksheets and grouped the possible bias (selection, detection, attrition, reporting, baseline imbalance, incorrect analysis) and confounders in 4 diagrams: mortality, blood product replacement, blood loss and deleterious effect of the use of the intervention (**Figure 4**). Publication bias couldn't be assessed.

RESULTS

We did a narrative and table synthesis of the outcomes (**Table 2**).

Results of the search

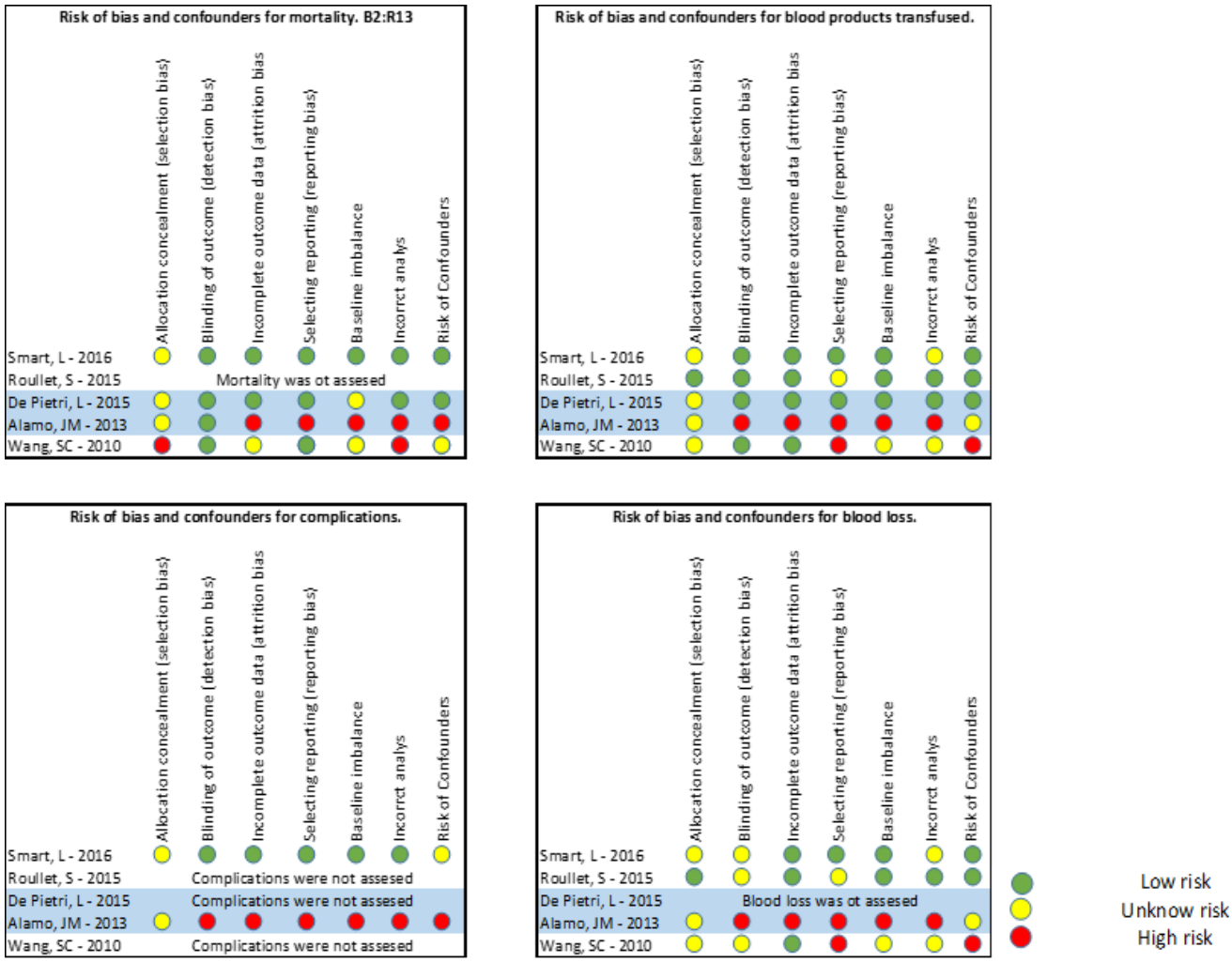
[3] EPOC - Cochrane Effective Practice and Organizational of Care WORKSHEETS FOR PREPARING A Summary of Findings (SoF) table.

We found 183 studies that met the searching criteria and 52 were possible relevant. After the abstract screening, we selected 8 studies for full text revision, but only 6 were available [16, 17, 18, 27, 29, 28](**Appendixes 2** and **3**). Three studies were excluded as we explained previously, and 3 studies were analysed in the results.

Risk of bias of individual studies

The result of assessing the bias is presented as a figure with 4 diagrams in that summarises the risk for each group of outcomes studied. **Figure 2**.

Figure 2: Description of the risk of bias.



Description of the studies

The 3 studies included [16, 18, 28], reported outcomes from adult LTX patients and were conducted from the intraoperative period. One is a quasi-randomised trial and two are non-RCT well designed with medium to low risk of bias, though we analyse all together and decide not to stratify the results. The sample sizes are 68, 60 and 24 patients. Authors report that TEG/ROTEM protocols were used to guide the blood products replacement, but the algorithm was not explained in Wangs' study. The control groups had specific triggers from standard laboratory coagulation tests (haemoglobin levels, platelets count, INR value) to replace blood products.

One study [16] included the first 24 postoperative hours for the transfusion results. Smart el all. reported mortality at 60 days and Wang et all. at 3 years, so aggregation was impossible.

Description of the outcomes

Mortality. None of the 2 studies that report mortality (60 days and 3 years) could demonstrate a difference between groups. The number of patients included was very small for the expected mortality in LTX and the risks of bias and confounders for this outcome was considered high to moderate in both studies. **Figure 2**.

Blood products transfused. None of the studies reported a reduction or increase of on PRC or platelets transfusion in the intraoperative period. Roullets' study showed an increase of the requirements of platelets in first 24 hours.

The transfusion of FFP was reduced in the intervention group in the two studies: Wang, 21.5(SD-12.7) to 12.8(SD-7) unites and Smart, 6.5 (IQR:4-14) to 4(IQR:4-7) units. Roullet et all, report lower amount of intraoperative transfusion of FFP, 8 (IQR:7-8) vs. 4(IQR:4-5), but after 24 hours there was not any difference.

The fibrinogen transfusion was studied by Roulette and even it was higher in the intraoperative period in the ROTEM group, the total amount transfused after 24 hours was similar in both groups.

Cryoprecipitates concentrates were studied in Smarts' study and suggested an increase in the intervention group from 1 to 2 units.

So, we can summarize that with a medium level of evidence, the decrees in blood product transfused in TEG/ROTEM groups are very likely to be limited to FFP, and possibly to the intraoperative period. After 24 hours, the number of patients exposed to blood products may not be affected by the use of TEG/ROTEM.

Blood loss. Smarts' study (with intermediate risk of bias [18]) showed less bleeding in the ROTEM group, but that findings were not confirmed in Roullet or Wang. So, we do not have evidence to say that the TEG/ROTEM directed therapy influences blood loss in adult LTX surgery. The main risk of measurement bias arises from difficulty of estimate intraoperative blood loss and the lack of blindness.

Complications and adverse events. None of the studies assessed the possibilities of complications and morbidity. Smarts' study compares hospitalization and ICU length of stay and couldn't demonstrate any differences between groups.

Costs. The costs were only analysed in one study [18] and the data are considered not to be generalizable. (**Table-2**).

Table 2: Summary of findings in the three studies reviewed with a summary of possible bias and confounders.

Author, year, country and reference.	Study design, sample size, time of follow up.	Summary: Selection	Confounding	Data collection	Blinding	Data analysis	Overal grade	Summary of resoults.
Laura Smart 2016 USA, (30)	Non-RCT, consecutive groups. ROTEM group: prospective and CCT retrospective. N=68	🟡	🟢	🟢	🟡	🟡	🟡	The ROTEM group had less intra-operative blood loss (2.0 vs. 3.0 L) and FFP transfusion (4 units vs. 6.5 units). The number of patients transfused cryoprecipitate was increased in ROTEM and platelet was not afected. The direct cost of blood products + tests was reduced in the ROTEM group ($113,142.89 vs. $127,814.77).
Stephanie Roulet 2015 France (31)	Non-RCT, consecutive groups. ROTEM group: prospective and CCT retrospective. N=60	🟡	🟢	🟢	🟡	🟢	🟢	There was not a decrease in blood transfusions and even FFP was less transfused during the intraoperative period. At 24 hours there was no diference in the number of patients exposed to blood products.
SC Wang 2010 Taiwan (29)	Near-RCT. TEG VS. CCT. N=28	🟡	🔴	🟡	🟡	🔴	🟡	In the TEG group, less FFP was used (mean [SD], 12.8 [7.0] units vs 21.5 [12.7] units). There were no differences in blood loss and 3-year survival. There was no differences in PRC or Platelet transfusion.

🟢 Low risk
🟡 Unknow risk
🔴 High risk

Discussion

We use a systematic approach to analyse the findings of 3 studies: one quasi-randomized and two non-RC. The inclusion of non-RCT increases the risks of potential biases (specially selection). In this study concerns arise with respect to differences between groups (selection bias) and from studies that do not explicitly explain the transfusion protocol used (reporting bias).

Altogether, the analyses, suggest a benefit of using a TEG/ ROTEM-guided transfusion therapy to reduce the transfusion of FFP in adult LTX. The reduction in other blood products transfused are not proven in these studies. Better designed studies with more number of patients are needed to assess the benefits of TEG/ROTEM in bleeding.

Our results differ from other systematic reviews conducted recently by Wikkelsø [(31)] that concluded that TEG/ROTED guided transfusion may reduce the need for blood products in patients with bleeding. The differences may be due to the different setting (mainly cardiac surgery) or the few number of studies and patients included in this review.

De Pietri compared the use of fibrinogen functional TEG (FF-TEG) vs. ROTEM [(29)] on resource consumption in 386 LTX patients. They concluded FF-TEG guided therapy reduces all blood products used (FFP, PRC and platelets) and an increase of fibrinogen use. This study might be a consideration when performing new studies about the utility of TEG.

The influence in mortality could not be demonstrated. The LTX surgery is extremely complex and it is likely that a lot of confounders make it difficult to assess mortality in this study with a small number of patients included.

In conclusion, TEG/ROTEM directed blood products replacement in LTX might be effective in reducing FFP transfusion during the intraoperative. Further studies are required to confirm this finding and to assess the overall requirements of other blood products, bleeding mortality and complications.

Reviews' limitations and reflections

Given the retrospective nature of the reviews, it would have been important to publish or register a formal protocol previously to perform the study (as done in the Cochrane reviews) to reduces biases. If there are later changes in the inclusion criteria, they must be duly justified[25]. We should have hand-search the reference list from identified relevant studies and contact the manufacturers of TEG and ROTEM for unpublished trials. If I would have need to contact Sujka, J or would purchase the paper for assess inclusion criteria [32]. A meta-analysis could have been done. For dichotomous data with binary outcomes we can calculate the risk ratios (RRs) with 95% CI and for continuous data the standardized mean difference. When the distribution is asymmetric the median value might be used.

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APENDIX 1 (A, B, C, D, E): Search strategy applied to 5 databases:

APENDIX 1 (A)

Database: Ovid MEDLINE 1946 -February week 5 2018 (Through the LSHTM Resources-Databases)		
#	Search Strategy	#ʳ of articles
1	Liver Transplantation/ or LIVER TRANSPLANT*.mp.	59,668
2	Thrombelastography/ or TEG.mp.	5,026
3	Thrombelastography/ or ROTEM.mp.	4,670
4	2 or 3	5,153
5	Haemorrhage/ or Blood Loss, Surgical/ or BLOOD LOSS.mp. or Postoperative Haemorrhage/	114,519
6	BLOOD TRANSFUSION/ or ERYTHROCYTE TRANSFUSION/ or TRANSFUSION MEDICINE/ or BLOOD COMPONENT TRANSFUSION/ or PLATELET TRANSFUSION/ or TRANSFUSION-RELATED ACUTE LUNG INJURY/ or BLOOD TRANSFUSION, AUTOLOGOUS/ or TRANSFUSION*.mp.	128,442
7	MORTALITY.mp. or MORTALITY/	590,479
8	costs.mp. or "Costs and Cost Analysis"/	211,936
9	5 or 6 or 7 or 8	988,540
10	1 and 4 and 9	81

APENDIX 1 (B)

Database: PubMed - US National Library of Medicine National Institutes of Health https://www.ncbi.nlm.nih.gov/pubmed/		
#	Search Strategy areas:	
1	LIVER TRANSPLANT*	
2	ROTEM OR TEG OR THROMBOELASTOGRAPHY	
3	TRANSFUSION OR BLEEDING OR BLOOD LOSS OR PLATELETS OR RED CELLS OR PLASMA OR MORTALITY	
4	COSTS	
	(ROTEM OR TEG OR THROMBOELASTOGRAPHY) AND (LIVER TRANSPLANT*) AND (TRANSFUSION OR BLEEDING OR BLOOD LOSS OR PLATELETS OR RED CELLS OR PLASMA OR MORTALITY OR COSTS)	
5	1 AND 2 AND (3 OR 4)	166

APENDIX 1 (C)

Database: LILACS (Latin American and Caribbean Health Sciences Literature) since 1982 http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i&form=F		
#	Search Strategy areas:	
1	liver transplantation OR hepatic transplantation OR liver transplant [Words]	
2	TEG OR ROTEM OR THROMBOELASTOGRAPHY [Words]	
3	COST [Words]	
4	BLEEDING OR TRANSFUSION OR MORTALITY OR OUTCOME [Words]	
	(ROTEM OR TEG OR THROMBOELASTOGRAPHY) AND (LIVER TRANSPLANT*) AND (TRANSFUSION OR BLEEDING OR BLOOD LOSS OR PLATELETS OR RED CELLS OR PLASMA OR MORTALITY OR COSTS)	
5	1 and 2 and (3 or 4)	3

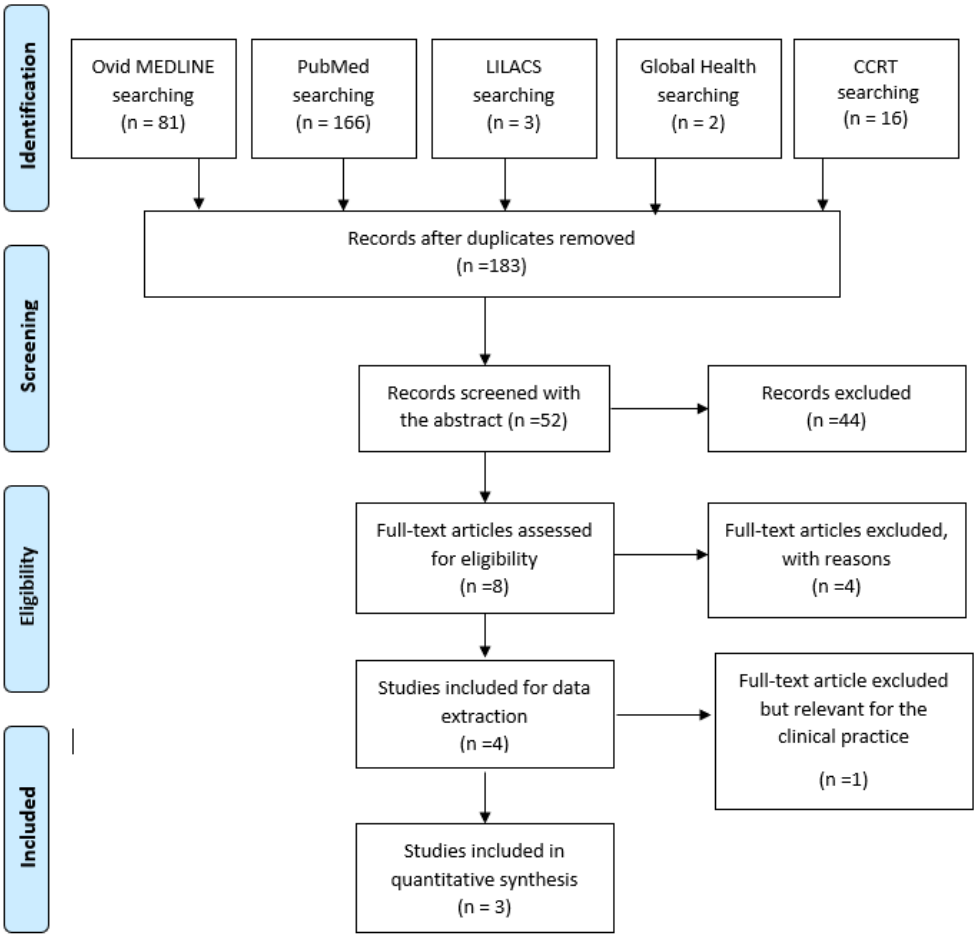
APENDIX 1 (D)

Database(s): Global Health 1910 -Week 5 February 2018 (Through the LSHTM Resources-Databases)		
#	Search Strategy	#ʳ of articles
1	Liver Transplantation/ or LIVER TRANSPLANT*.mp.	5,022
2	Thrombelastography/ or TEG.mp.	477
3	Thrombelastography/ or ROTEM.mp.	15
4	2 or 3	490
5	Haemorrhage/ or Blood Loss, Surgical/ or BLOOD LOSS.mp. or Postoperative Haemorrhage/	2,062
6	BLOOD TRANSFUSION/ or ERYTHROCYTE TRANSFUSION/ or TRANSFUSION MEDICINE/ or BLOOD COMPONENT TRANSFUSION/ or PLATELET TRANSFUSION/ or TRANSFUSION-RELATED ACUTE LUNG INJURY/ or BLOOD TRANSFUSION, AUTOLOGOUS/ or TRANSFUSION*.mp.	128,442
7	MORTALITY.mp. or MORTALITY/	176,793
8	costs.mp. or "Costs and Cost Analysis"/	44,438
9	5 or 6 or 7 or 8	230,440
10	1 and 4 and 9	2

APENDIX 1 (E)

Databases: Cochrane Central Register of Controlled Trials (CCRCT) http://cochranelibrary-wiley.com/cochranelibrary/search		
#	Search Strategy areas:	
1	LIVER TRANSPLANT*	
2	ROTEM OR TEG OR THROMBOELASTOGRAPHY	
3	TRANSFUSION OR BLEEDING OR BLOOD LOSS OR PLATELETS OR RED CELLS OR PLASMA OR MORTALITY	
4	COSTS	
	(ROTEM OR TEG OR THROMBOELASTOGRAPHY) AND (LIVER TRANSPLANT*) AND (TRANSFUSION OR BLEEDING OR BLOOD LOSS OR PLATELETS OR RED CELLS OR PLASMA OR MORTALITY OR COSTS)	
5	1 AND 2 AND (3 OR 4)	16

Appendix 2: Modified from PRISMA diagram to search and screen relevant articles.



Appendix 3: Summary of the 8 studies selected for full text revision.

Four studies were excluded (grey shadow) and one was also excluded but was discussed briefly in the (light blue shadow).

	Year / Author / Journal	Title	Type of study	Exclusion criteria / considerations
1.	Wang SC Transplant Proc. 2010	Thromboelastography-guided transfusion decreases intraoperative blood transfusion during orthotopic liver transplantation: randomized clinical trial.	Near-RCT	No
2.	Roullet S Liver Transpl. 2015	Management of bleeding and transfusion during liver transplantation before and after the introduction of a rotational thromboelastometry-based algorithm.	Non-RCT (prospective)	No
3.	Smart L Ann Hepatol. 2017	Rotational Thromboelastometry or Conventional Coagulation Tests in Liver Transplantation: Comparing Blood Loss, Transfusions, and Cost.	Non-RCT (Prospective and retrospective)	No
4.	De Pietri L Transplant Direct. 2015	Reduced Transfusion During OLT by POC Coagulation Management and TEG Functional Fibrinogen: A Retrospective Observational Study.	Retrospective cohort observational study.	We consider this study relevant despite some considerations. * FF-TEG vs. TEG
5.	Alamo JM Transplant Proc. 2013	Is "intra-operating room" thromboelastometry useful in liver transplantation? A case-control study in 303 patients	Non-RCT. Unclear "match" between groups.	Not TEG/ROTEM guided algorithm. High risk of bias. Confounders were not assessed. Outcomes are not well defined
6.	Trzebicki J Ann Transplant 2010	The use of thromboelastometry in the assessment of haemostasis during orthotopic liver transplantation reduces the demand for blood products.	Retrospective non-RCT	TEG/ROTEM guided blood replacement by using antifibrinolytic drugs in the intervention group.
7.	Sujka J Pediatr Transplant. 2018	The impact of thromboelastography on resuscitation in paediatric liver transplantation.	Unknown	Full text article not founded *(Author contact, LSHTM, Journal site searched)*
8.	Plevak D Transplant Proc. 1993	Blood product transfusion therapy after liver transplantation: comparison of the thromboelastogram and conventional coagulation studies.	Unknown	Full text article not founded *(Author contact, LSHTM, Journal site searched)*

*The comparative group is "TEG without functional fibrinogen" detection component.

Appendix 4: Quality assessment domain and the relative weigh that we considered for this review.

Domain	Description	Weigh
Intervention	Description of the intervention, the implementation and the consequences in decision making (protocolization).	High
Data collection	Most of the outcomes are easy measurable (mortality, amount of blood products transfused), but other outcomes (blood loss, complications) must be well described and defined if we would like to aggregate them between studies.	High
Data analysis	We mainly assesed the baseline situation of the two groups compared and the confounders. Not intention to treat was done or statistical analysis for metanalysis.	Intermediate
Allocation and blinding	The nature of these studies (diagnostic intervention - TEG or ROTEM) at the point of care, where the same anaesthesiologist that perform the diagnostic have the full responsibility for the care of the patient (and the decision of blood transfusion) makes the blinding impossible. We will not consider this point as an important issue.	Low
Sampling and recruitment	To decide the use or not use of a potential lifesaving equipment (advantages proven in other clinical scenarios) may be consider unethical if the patient is bleeding and some advantage can be obtained from the TEG/ROTEM at the operating room (OR). So, randomization might be difficult to justify and the comparison between groups of patients with vs. without availability is reasonable.	Low

Appendix 5 (A, B, C, D, E): Worksheets for data collection of the five studies that underwent quality appraisal and data extraction.

Study included for summary of results.

APPENDIX 5 (A)

Wang, SC - 2010							
Title	Thromboelastography-Guided Transfusion Decreases Intraoperative Blood Transfusion During Orthotopic Liver Transplantation: Randomized Clinical Trial						
Method	RCT- The randomization was not explained.						
Objectives	To assess the impact of intraoperative TEG use, inblood products administrate and long term (3 years) survavial in LTX patients.						
Participants	24 LTX patients; 12 in each group. No explanation of inclussion or exclussion criteria.						
Period of study, from intervention to follow up	From 2005to 2006						
Intervention	TEG vs. CCT to guide blood product replacement. Protocol based.						
Outcomes		**TEG N=12**	**SD**	**CCT N=12**	**SD**	**P value**	**Coments on analysis and statistics**
Primary (for owr review)	3-year survival	2 patients		3 patients			N° of patients small for statistic analysis
	Transfused products (Nonparametric test Wilcoxon)						
mean (SD)	PRC (units)	16.7	12.80	14.2	7.1	p>0.05	No of patients small for statistic analysis
	FFP (units)	21.5	12.7	12.8	7	p<0.05	No CI was calculated and unknown if extreme data were excludded. Assumed normal distribution (mean and SD).
	Platelets (units)	30.1	18.5	27.3	13.9	p>0.05	
	Cryo. (units)	15.6	9.5	13	10.3	p>0.05	
Secondary	Blood loss (mL)	6328	3704	4776	4264	p>0.05	No specification of how to meassure it.
Other results	Albumin (mL)	664	475	829	588	p>0.05	Unknown the concentration.
Notes	Sample size was calculate to provide 80% power to demonstrate the influence of ROTEM in decreasing intraoperative blood loss.						

Risks of bias		
Bias	**Authors' judgement**	**Suport for judgement**
Group allocation (selection bias)	High risk	Do not specify randomization method.
Blinding of outcomes assesment (detection bias)	High risk	Not blinded in any way.
Incomplete outcomes (attrition bias)	Low risk	All outcomes are reported in both groups, no patient seems to be excludded.
Selective reporting (reporting bias)	High risk	No complications or bad outcomes assessed.
Baseline imbalance	Unknown risk	Only Age, sex, BMI and MELD was assessed.
Incorrct analys	Unknown risk	Statistic methods are poor explained and means are used for unlikely normal distribution variables.
Other bias		
Risk of Confounders	**Authors' judgement**	**Suport for judgement**
Temperature, hb, Ca control	Unknown risk	Aouthors establish that there is a correction of all factors previously to transfusion.
Protamine and Aminocaproic acid	Unknown risk	Could not be compared with the control group.
Surgical technique	Unknown risk	Does not specify if they change the surgical technique.
Anesthesia technique	Low risk	Anesthesia medication and monitoring reported to be the same.
Team experience and skills	Unknown risk	The authors said that the study was limited in time to minimize changes in "institutional practices".
Donor (quality of liver, LD, DD)	Unknown risk	Unknown type or characteristics of the donnors.

APPENDIX 5 (B)

Study included for summary of results.

Roullet, Stephanie - 2015								
Title	Management of Bleeding and Transfusion During Liver Transplantation Before and After the Introduction of a Rotational Thromboelastometry–Based Algorithm							
Method	Non randomized - Observational (Consecutive groups) ROTEM group: prospective and CCT retrospective.							
Objectives	To evaluate the impact of a ROTEM-based transfusion algorithm on transfusions and bleeding during OLT.							
Participants	60 LTX patients; adults (30 in each group)							
Period of study, from intervention to follow up	From June 2012 to June 2013.							
Intervention	ROTEM vs. CCT to guide blood product replacement (2012-2014). Protocol based.							
Outcomes		ROTEM N=30	IR	CCT N=30	IR	P value	Coments on analysis and statistics	
Primary (for owr review)	Transfused products (Nonparametric test Wilcoxon)							
	Autologus transfusion	490	268- 1122	545	288- 752	P=625		
Expresed as median and interquartil range	PRC (units)	4	3-6	5	3-7	p>0,05		
	PRC (patients)	24		22		p>0,05		
	FFP (units)	8	7-8	4	4-5	p<0.05	**No differences at 24 hours postoperative.**	
	FFP (patients)	4		10		p>0,05		
	Platelets (units)	1	1.0.1.0	1.1	1-1.25	p>0,05	**But in the postoperative period the patients receive more platelets**	
	Platelets (patients)	11		12		p>0,05		
	Fibringen (g)	6.0	4.5-7.5	4	3-4.5	p>0,05		
	Fibrinogen (patients)	9		17		p<0.05	**No differences at 24 hours postoperative.**	
Secondary	Bleeding (L)	3	1.7 - 4.0	3	2.1 - 4.8	P=0.390		
	4% Albumin (bottels)	6	5 - 8	7	5- 10	p=0.625		
Other results	**Protrombine rate %**	**28**	**20-39**	**44**	**32-60**	**p=0.001**	**No differences at 24 hours postoperative.**	
Notes	Sample size was calculated: 14 patients per group should provide 80% power to demonstrate the influence of ROTEM on increasing fibrinogen transfusions during OLT. The authors used 30 patients per group.							
	When comparing the total transfusion in 24 hours (intraoperative + early postoperative period) there is no differences in any blood product transfused perioperatively.							

Risks of bias		
Bias	**Authors' judgement**	**Suport for judgement**
Group allocation (selection bias)	Low risk	Consecutive groups. Prospective. Standarised anesthesia and surgery.
Blinding of outcomes assesment (detection bias)	High risk	Not blinded in any way.
Incomplete outcomes (attrition bias)	Low risk	All outcomes are reported in both groups, no patient seems to be excludded.
Selective reporting (reporting bias)	Unknown risk	Not assesment of bad outcomes.
Baseline imbalance	Low risk	No differences in characteristics of the groups
Incorrct analys	Low risk	Statistic is well detailed and methods described in deep.
Other bias		
Risk of Confounders	**Authors' judgement**	**Suport for judgement**
Temperature, hb, Ca control	Low risk	Aouthors protocolize end point for this confounders.
Protamine and Aminocaproic acid	Low risk	Protocolization of use.
Surgical technique	Low risk	Piggi Back for all patients.
Anesthesia technique	Low risk	Protocolization of anesthesia.
Team experience and skills	Low risk	The same group of surgeons and anaesthesiologists.
Donor (quality of liver, LD, DD)	Low risk	DD in all patients, similar characteristics in both groups.

APPENDIX 5 (C)

Study included for summary of results.

Smart, Laura - 2016							
Title	Rotational Thromboelastometry or Conventional Coagulation Tests in Liver Transplantation: Comparing Blood Loss, Transfusions, and Cost.						
Method	Non randomized - Observational (Consecutive groups) ROTEM group: prospective and CCT retrospective.						
Objectives	To assess the impact of a ROTEM-guided protocol on intraoperative blood loss during LTX and assess transfusional requirements, in comparison with conventional coagulation tests.						
Participants	68 LTX patients; older than 18 years (34 in each group)						
Period of study, from intervention to follow up	From 2012 to 2014						
Intervention	ROTEM vs. CCT to guide blood product replacement (2012-2014). Protocol based.						
Outcomes		ROTEM N=34	CI IQR	CCT 34	CI IQR	P value or ODD ratio	Coments on analysis and statistics
Primary (for owr review)	Mortality 60 days	2 patients		2 patients		OR =1	
Expresed as median and interquartil range	Transfused products (Nonparametric test Wilcoxon)						
	PRC (units)	5.5	2 to 11	8	4 to 16	p=0,07	Saved retransfused blood was includded
	FFP (units)	4	4 to 7	6.5	4 to 14	p=0.02	
	Platelets (units)						
	Cryo. (units)	2	0 to 3	1	0 to 2	p=0.04	
Secondary	Morbidity and complications						
	Thrombotic events						
	Other:						
	Bleeding (mL)	2000	1500-3375	3000	2000-77500	p=0.04	
	Hospitalization	NR		NR		NR	Said "no differences"
	ICU staying	3	2 to 3	3	1 to 3	NR	Said "no differences"
	Costs (USD) total =	113,143		127,814			Costs calculated from OSUWMC's (*)
	blood products =	103786		123067			Consider cost of CCT = ROTEM
	monitoring=	9,356		4,747			
Other results	Postop. INR	2,0		1,7		p=0.002	Does not specify CI or SD.
	Platelets	98,000		63,000		p=0.002	
Notes	Sample size was calculate to provide 80% power to demonstrate the influence of ROTEM in decreasing intraoperative blood loss.						

Risks of bias		
Bias	**Authors' judgement**	**Suport for judgement**
Group allocation (selection bias)	Unknown risk	Consecutive groups. Retrospective control group. Standarised anesthesia and surgery.
Blinding of outcomes assesment (detection bias)	High risk	Not blinded in any way.
Incomplete outcomes (attrition bias)	Low risk	All outcomes are reported in both groups, no patient seems to be excludded.
Selective reporting (reporting bias)	Low risk	Good and bad outcomes were reported
Baseline imbalance	Low risk	No differences in characteristics of the groups
Incorrct analys	Inknown risk	
Other bias		
Risk of Confounders	**Authors' judgement**	**Suport for judgement**
Temperature, hb, Ca control	Low risk	Aouthors establish that there is a correction of all factors previously to transfusion.
Protamine and Aminocaproic acid	Unknown risk	Could not be compared with the control group.
Surgical technique	Unknown risk	Does not specify if they change the surgical technique.
Anesthesia technique	Low risk	The same protocol in both groups.
Team experience and skills	Low risk	The same group of surgeons and anaesthesiologists.
Donor (quality of liver, LD, DD)	Unknown risk	DD in all patients, unknown characteristics of the donnors.

APPENDIX 5 (D)

Study excluded from the results but considered for the discussion.

De Pietri, Lesly - 2015							
Title	Reduced Transfusion During OLT by POC Coagulation Management and TEG Fibrinogen: A Retrospective Observational Study						
Method	Retrospective cohort observational study. Patients between a d after the introduction of the new methot: FF-TEG.						
Objective	To assess the impact on resource consumtion of the usage of a new coagulation FF-TEM vs TEM in LTX patients.						
Participants	386 LTX and LTX+Kidney transplant and re-transplantataion. The 3 types of transplants were stratified for analysis.						
Period of study, from intervention to follow up	From 2005 to 2014						
Intervention	FF-TEG vs. TEG (not distinguish between the contribution of fibrinogen or platelets to cuagulum formation. The authors used diferent algoritms based on the interventions (FF-TEG or TEG)						
Outcomes (mean, SD or %) **The same findings were confirm in the 3 stratification groups.**		FF-TEG N=256	SD	TEG N=117	SD	P value	Coments on analysis and statistics
Primary (for owr review)	Mortality 30 days	2.75%		2.56%		p>0.05	
	Mortality 60 days	10.16%		12.82%		p>0.05	
	Transfused products (Nonparametric test Wilcoxon)						
Expresed as median and interquartil range	BLOOD (mL)	1502	1376.00	794	707	p<0,001	Homologous blood
	FFP (mL)	537	797	98	374	p<0.001	
	Platelets (mL)	159	279	75	148	p<0.005	
	Albumin (mL)	190	104	198	67	P=0.15	
	Fibrinogen (mL)	0.1	0.5	1.4	1.8	p=0.04	
Other results	Other:						
	MELD score was hghly asociated with transfusions					MELD score was high in FF-TEG group what may increase the strenght of the asociation.	
Notes	Sample size was calculate to provide 80% power to demonstrate the influence of ROTEM in decreasing intraoperative blood loss.						

Risks of bias		
Bias	**Authors' judgement**	**Suport for judgement**
Group allocation (selection bias)	Unknown risk	Consecutive groups. Retrospective control group. Standarised anesthesia and surgery.
Blinding of outcomes assesment (detection bias)	High risk	Not blinded in any way.
Incomplete outcomes (attrition bias)	Low risk	All outcomes are reported in both groups, no patient seems to be excludded.
Selective reporting (reporting bias)	Low risk	Good and bad outcomes were reported
Baseline imbalance	Low risk	No differences in characteristics of the groups
Incorrct analys	Low risk	Statistic well explained and detailed. Multivariable analysis was performed.
Other bias		
Risk of Confounders	**Authors' judgement**	**Suport for judgement**
Temperature, hb, Ca control	Low risk	Aouthors establish that there is a correction of all factors previously to transfusion.
Protamine and Aminocaproic acid	Unknown risk	Unknown
Surgical technique	Low risk	Sthe same techneeque and the same team.
Anesthesia technique	Low risk	Sthe same techneeque and the same team.
Team experience and skills	Low risk	The same group of surgeons and anaesthesiologists.
Donor (quality of liver, LD, DD)	Unknown risk	DD in all patients, unknown characteristics of the donnors.
Type of surgeries	Low risk	Patients were tratified to analysis in LXT - LKT and re-LTX

FF-TEG: fibrinogen functional TEG (includes and algorrithm to transfuse fibrinogen when it is needed).

APPENDIX 5 (E)

Study excluded due to the high risk of bias and confounders, and due to the impression definition of the outcomes.

Alamo, JM - 2013

Title	Is “Intraeoperating Room” Thromboelastometry Useful in Liver Transplantation? A Case-Control Study in 303 Patients
Method	Non randomized - Observational (Consecutive patients) ROTEM group: prospective and CCT retrospective.
Objectives	To estimate the influence of TEM on graft survival, morbidityand mortality after LTX.
Participants	303 LXT patients. Do not desribe age or type of graft received.
Period of study, from intervention to follow up	Unknown
Intervention	TEM vs. Non-TEM in diferent groups of bleeding risk: PGR (risk of preoperatori blleding) and LP (= or more than 5 PRC administred intraoperative) Unclear regarding of the overlap of groups or the patients in group PGR that received more than 5 unts RBC.

Outcomes	Main groups	PEG		PT			
	Comparative intervention	TEM N=57	Non-TEM N=66	TEM N=32	Non-TEM N=80	P value	Coments on analysis and statistics
Primary (for owr review)	Early mortality	"lower"		"lower"		0,076	Not defined"Earaly mortality" But "not significant"
Secondary (for owr r	PRC (units)	"lower"		"lower"		<0,05	
	Bleeding (mL)	lower		No report	No report		
	Renal failure	lower		No report	No report		The authors did not define the outcomes clearly (defination of what is cosidered PNF, RS, renal failure, etc.
	PNF	lower		lower			
	Surgical complications	lower		lower			
Other results	Reperfusion sd,			lower			

Notes **There was not a deep analysis of the resoult neither an explanation about why the authors choose those outcomes.**

Risks of bias

Bias	**Authors' judgement**	**Suport for judgement**
Group allocation (selection bias)	Unknown risk of bias	4 groups allocation 2 groups related to some preoperative bleeding risk factors 2 groups related to number of number of PRC
Blinding of outcomes assesment (detection bias)	High risk	Not blinding
Incomplete outcomes (attrition bias)	High risk	Not know if every patients was studiesd for every outcome.
Selective reporting (reporting bias)	High risk	Unknown: many otcomes are not defined.
Baseline imbalance	High risk	
Incorrct analys	Unknown risk of bias	
Other bias		

Risk of Confounders	**Authors' judgement**	**Suport for judgement**
Temperature, hb, Ca control Protamine and Aminocaproic acid Surgical technique Anesthesia technique Team experience and skills Donor (quality of liver, LD, DD)	High risk	The study does not consider any of the confounders in any of the groups.