META-ANALYSIS

Mortality in liver transplant recipients with portal vein thrombosis – an updated meta-analysis

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SUMMARY

Portal vein thrombosis (PVT) is the most common thrombotic event in liver transplant (LT) recipients, but its impact on mortality after LT has been analyzed in heterogeneous cohorts with mixed results. To conduct a meta-analysis on the impact of PVT on post-LT survival. A systematic search was conducted on studies (published from January 1986 to January 2018) that reported 30-day and 1-year mortality after LT of PVT patients. Four hundred twenty-seven articles were reviewed and 44 were included. Among 98 558 LT, 7257 (7.3%) involved patients with PVT. The mean quality was high (7.1 on the Newcastle–Ottawa scale). The 30-day pooled mortality rate was higher for patients with PVT (64/490; 13%) than for others (259/3357; 7%) (OR 2.29; 95% CI 1.43–3.68; $P < 0.0001$). One-year mortality was likewise higher in recipients with (853/6302; 13.5%) than in those without PVT (7476/75 355; 9.9%) (OR 1.38; 95% CI 1.14–1.66; $P < 0.0001$). Heterogeneity wasn't significant (I^2 46% and 65%). Patients whose PVT was complete had a higher 30-day pooled mortality rate (OR 5.65; 95% CI 2–15.96; $P < 0.0001$), and a 1-year mortality rate (OR 2.48; 95% CI 0.99–6.17; $P = 0.38$) than patients with partial PVT. PVT is common in LT candidates and it is associated with higher short- and medium-term mortality after LT.

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Key words
cavoportal hemitransposition, liver cirrhosis, liver transplantation, portal vein thrombosis

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Introduction

Portal vein thrombosis (PVT) is a common complication in patients with cirrhosis, with a reported prevalence of up to 28% in liver transplant candidates [1]. Cirrhosis itself is now recognized as a hypercoagulable disease that, combined with a low portal venous flow in the setting of portal hypertension, is one of the main risks relating to the onset of PVT [2]. The impact of PVT on the natural history of liver disease and portal hypertension varies and conflicting results have been published in the literature [3–5]. There is consequently no consensus on its optimal management in patients with cirrhosis [6]. PVT has been found more common in patients with advanced cirrhosis (Child Class C), and possibly with more severe portal hypertension – in other words, in potential candidates for liver transplantation (LT) [7]. PVT is no longer a contraindication for LT, however, the development of various surgical and medical strategies has meant that patients with thrombosis confined to the portal vein (PV) can undergo LT with results that are comparable with those of

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transplant recipients without PVT [8,9]. On the other hand, some studies have found a higher post-LT mortality among patients with complete thrombosis of the main portal vein. In a retrospective analysis of 21 673 LT recipients in the United Network for Organ Sharing (UNOS) registry, the presence of PVT was identified as an independent risk factor for post-transplant mortality [10]. This was especially true in patients with more extensive thrombosis necessitating a nonanatomical reconstruction of their PV inflow [11]. The question of the safety and efficacy of performing LT in patients with complete PVT, especially when it extends to the superior mesenteric vein (SMV), remains to be answered with confidence. The aim of the present study was thus to fill this gap by meta-analyzing the results of nonrandomized studies reporting on the short- and long-term outcomes of patients who received an LT in the presence of pre-existing PVT.

Methods

In planning our systematic review, the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [12] guidelines were adopted for the meta-analysis, as they are more appropriate in the current setting than the Quality of Reporting of Meta-analyses (QUOROM), or Transparent Reporting of Evaluations with nonrandomized designs (TREND) [13].

Study design

Prospective or retrospective nonrandomized comparative studies (NRCS) reporting short- and long-term outcomes of LT in patients with and without PVT were considered for the meta-analysis. Most of the NRCS considered were retrospective cohort studies or historical control studies.

Study group and PVT classification

Portal vein thrombosis was defined as a thrombus occupying the portal lumen, which can affect the intrahepatic as well as the extrahepatic venous tracts. When feasible, PVT was classified as complete or partial, or according to Yerdel's classification [14], which is considered the most adequate because it best correlates thrombosis extension with surgical technique and outcome. The classification considers four grades: grade I, a thrombus occluding <50% of the portal vein, with or without minimal obstruction of the SMV; grade 2, a >50% occlusion of the PV, including total occlusions, with or without minimal extension into the SMV; grade 3, a complete thrombosis of both the portal vein and the proximal SMV, with distal SMV remaining open; and grade 4, complete thrombosis of the portal vein and the proximal and distal SMV.

Search strategy, inclusion, and exclusion criteria

A systematic search was run in MEDLINE, EMBASE, and Science Citation Index using the following terms: (portal vein) OR (mesenteric) OR (splanchnic thrombosis) AND (liver transplantation). All studies published between January 1986 and January 2018, in the English language and concerning humans, were considered for this review. Only articles published after 1990 were used for the analysis because of major changes intervening in surgical techniques (e.g., eversion instead of blind venous thrombectomy). Most studies published before 1990 contained few cases because PVT had previously been a considered a contraindication to LT. The prevalence of PVT among LT candidates was consequently artificially low because patients with PVT were removed from the waiting list. Finally, most of the studies published before 1990s included cases that were later published again as updates on PVT management at the centers concerned. Duplicate publications and articles not reporting adequate summaries of the original raw data were ruled out. Other inclusion criteria were: studies reporting the incidence of PVT in cirrhotic patients awaiting LT; studies reporting the prevalence of PVT as an operative finding; studies at least roughly classifying the severity of patients' PVT; studies in which PVT was graded; studies reporting surgical and medical approaches to PVT management; and studies reporting the outcome of patients' PVT after LT. Studies that included partial LTs, case reports, and studies describing less than five LTs in the presence of underlying PVT thrombosis were not considered for this review. Studies focusing exclusively on pediatric populations were excluded too, while pediatric patients in comprehensive series were excluded from the analysis. Series and individuals within series with neoplastic thrombosis were likewise excluded. The full papers of the articles included were reviewed, retrieving and analyzing the following key variables (among others): total number of LTs performed; number of LTs involving patients with PVT; study period; classification of PVT; prevalence of PVT; outcomes in terms of 30-day mortality and 1-year patient survival; and recurrence of PVT after LT.

Quality assessment and risk of bias from individual studies

Most of the studies included in the meta-analysis were observational, so the Newcastle–Ottawa scale (NOS) was used to the judge methodological quality [15]. The items to consider included patient selection, comparability of cases and controls, and exposure/outcome. The NOS overall quality scores range from 0 to 9, and are grouped into three levels: low quality, NOS score <4; moderate quality, 4≤ NOS score <7; and high quality, NOS score ≥7). Two reviewers independently appraised the studies. Interpreter agreement was assessed using the correlation coefficient r. Disagreements were resolved by discussion and consensus. As there was no cutoff for study quality, the studies were divided into three groups approximating those mentioned above.

Statistical methods

Dichotomous data were analyzed using comprehensive meta-analysis. The pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using either or the Mantel-Haenszel method (fixed effects model) and the Der Simonian and Laird method (random effects model). Chi-square for heterogeneity was used to assess the variation on treatment effect within trials. We assumed heterogeneity if $P < 0.1$. Publication bias was assessed using a funnel plot for standard error by effect size (log OR). All statistical analyses were run and plots were obtained using dedicated software (RevMan 5).

Results

Search results

In all, 427 articles were initially retrieved for abstract review (Fig. 1), after which the following articles were excluded: three were reports on the same series, so only the latest report was considered [16–18]; five were not in the English language; two were animal studies; 12 referred exclusively to pediatric cases; 35 were single-case reports or small case series (<5 cases); and 229 did not meet our inclusion criteria because they were opinion-based reports, studies performed outside the LT setting, or only described Budd–Chiari patients. Furthermore, studies concerning patients with hepatocellular carcinoma (HCC) were also excluded, as HCC is a separate cause of portal and splanchnic vein thrombosis, requiring a different management strategy and carrying a different prognosis. Finally, eight studies were single-center updates on LT series that included previously published cases, so only the latest update was considered. Ultimately, there were 44 studies eligible for the systematic review, none of which were prospective.

Study quality – publication bias

As mentioned previously, the Newcastle–Ottawa quality scale was adopted wherever possible. The mean quality of the studies was 7.1 (range 6–8), which is a good overall rating (Table 1). As for publication bias, funnel plot analyses revealed no significant impact of selection bias on 30-day or 1-year mortality (Figs 2 and 3).

Prevalence at transplant and surgical technique

Amongst 98 558 LTs described in the studies considered, 7257 were performed in patients with PVT. The prevalence ranged from 2.1% in studies describing LT procedures performed before 1990 to 23.3% in more recent series (Table 2) [1,9,14,17,19–56]. The low prevalence reported by some authors may be attributable to different policies adopted at the various transplant centers resulting in patients with extensive thrombosis of the splanchnic vessels being excluded from the waiting list for LT. The time when the studies were published does not appear to have influenced the selection of candidates with PVT, however, because studies including patients undergoing LT before and after 2000 had a similar prevalence of this disorder. In 800 patients described in the 12 studies, PVT was neither characterized as "partial" or "complete", nor in any way that could relate to Yerdel's classification. Among 763 patients discussed in 21 studies, 422 had partial PVT (55.3%) and 341 had complete PVT (44.7%).

The surgical technique used to restore portal vein inflow in patients with grade 4 PVT was only described in six studies [14,43,57–60]. To be more specific, the surgical technique was reported for 46 cases, most of them involving cavoportal hemitransposition (19/41) 46%. The remainder were treated as follows: an extra-anatomical reconstruction without employing the venous conduit was performed in eight cases (20%); a collateral vessel was used in seven cases (16%); and a jump graft (using donor tissue) was performed in three cases (7%).

Mortality

In seven studies, the 30-day pooled mortality rate after LT was higher among patients with PVT (13%) than in

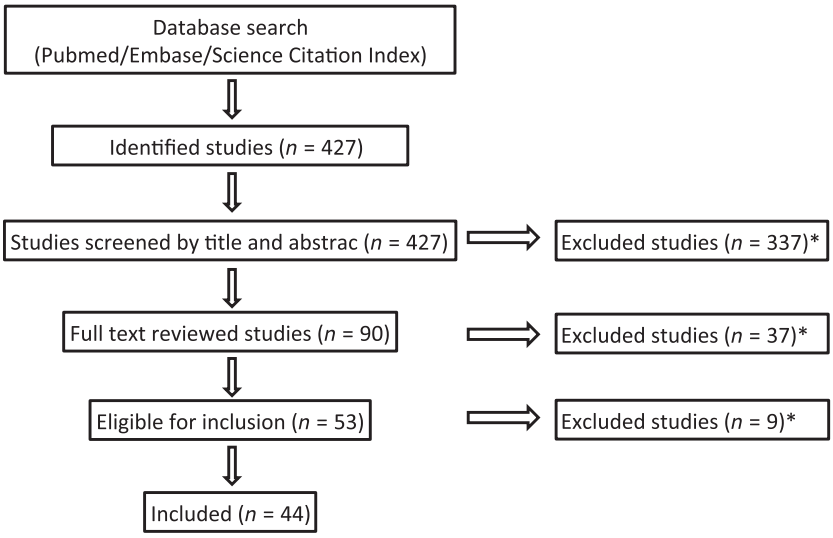

Figure 1 Search results: flow chart. *Reasons for exclusion:
- Did not meet the criteria for the meta-analysis (not separate patients with and without HCC, case series exclusively leading with Budd–Chiari syndrome, PVT in non cirrhotic patients (n = 324)
- More recent studies published on the same cohort (n = 4)
- Duplicated studies (n = 3)
- Animal studies (n = 2)
- Pediatric cohorts (n = 12)
- Case reports including less than five patients (n = 38).

cirrhotic patients without PVT (7%) (OR 2.29; 95% CI 1.43–3.68; $P < 0.0001$), with no heterogeneity between the studies (I = 46%; Fig. 4). Mortality at 1 year after LT was reported in 23 studies, and was again higher in patients with PVT (13.5%) than in those without thrombosis (9.9%) (OR 1.38; 95% CI 1.14–1.66; $P = 0.0008$) (Fig. 5). Pooling data from ten studies [14,26,39,43,45,57–61] that reported on mortality by grade of PVT, only three of the 128 patients with grade 1 PVT (2.3%), 8 of 137 with grade 2 (5.8%), and 3 of 35 with grade 3 (8.6%) were dead 30 days after LT. On the other hand, mortality rose to 9 out of 33 (27%) ($P < 0.001$) among patients whose PVT extended to the SMV (grade 4). Only, three studies [23,39,50] reported on 1-year mortality by extent of splanchnic vein thrombosis, describing a mortality of 15 out of 76 patients with a partial PVT (22%) and 19 out of 45 (42%) with a complete PVT ($P = 0.011$).

The 30-day pooled mortality rate was higher among patients with occlusive PVT than among those with partial PVT in four studies (OR 5.65; 95% CI 2–15.96; $P = 0.001$) (Fig. 6). Post-hoc Bonferroni analysis confirmed the significant difference in mortality between patients with complete versus partial PVT ($P = 0.002$). One-year mortality was also higher in patients with complete PVT (two studies), although the difference was only on the threshold of statistical significance (OR 2.48; 95% CI 0.99–6.17; $P = 0.05$) (Fig. 7). When possible, a subsequent analysis was performed on the studies including Yerdel's classification of PVT: only one study mentioned 1-year mortality, which was higher in patients with grades 3 and 4 PVT than for grades 1 or 2 [16/32 (50%) vs. 298/1649 (18%)]. Thirty-day mortality was also higher in patients with grades 3 and 4 PVT than in those with grades 1 and 2, although the difference was not statistically significant (OR: 7.87; CI 95% 0.48–129.88; $P = 0.15$) (figure not shown), probably due to the small cohorts analyzed.

Mortality after LT was then analyzed by time period, i.e., before (Group 1) and after (Group 2) the year 2005. This analysis could only be run for 1-year mortality. Nine and 13 studies were included in Groups 1 and 2, respectively, and the mean mortality rates were very similar (20.7% and 21.5%, respectively). The pooled mortality rate was higher for patients with PVT than for those without PVT both before 2005 (OR 1.49; 95% CI 1.08–2.06; $P = 0.02$) and afterwards (OR 1.54; 95% CI 1.33–1.78; $P < 0.00001$) (see Figures S1 and S2). Funnel plot analyses revealed no significant impact of selection bias (see Figures S3 and S4).

Table 1. Quality of studies included in the meta-analysis.

Study, year (reference)	Center	Study period	Total LT (n)	LT in PVT patients (n)	Prevalence (%)	Newcastle–Ottawa scale			Total score
						Selection	Comparability	Outcome	
Gao, 2016 [55]	Chin Liver Transplant registry	1993–2013	19856	1697	8.5	+++	+	++	6
Ghabril, 2016 [32]	Indianapolis, USA	2002–2013	50393	3321	6.6	+++	+	+++	7
Hibi, 2014 [34]	Miami, USA	1998–2009	1379	174	12.6	++++	+	+++	8
D'Amico, 2013 [53]	Modena, Italy	2000–2010	447	51	11.4	++++	+	+++	8
Ravaioli, 2011+ [45]	Bologna, Italy	1998–2008	889	91	10.2	++++	+	+++	8
Englesbe, 2010 [27]	Ann Arbor, USA	1995–2007	574	30	4.9	++++	+	+++	8
Suarez Artacho, 2010 [50]	Seville, Spain	1991–2008	670	48	7.16	+++	+	++	6
Shi, 2010 [48]	Chengdu, China	1999–2007	404	48	11.9	+++	+	+++	7
Doenecke, 2010 [23]	Regensburg, Germany	2004–2007	193	24	12.4	+++	+	+++	7
Tao, 2009 [51]	Shangai, China	2002–2006	465	42	9	++++	+	+++	8
Wu, 2009 [52]	Shenyang, China	1995–2007	194	24	12.3	+++	+	+++	7
Pan, 2009 [43]	Tianjin, China	1998–2007	2614	253	10.09	+++	+	+++	7
Gao, 2009 [30]	Beijing, China	2004–2008	308	46	14.9	+++	+	+++	7
Lendoire, 2007 [9]	Buenos Aires, Argentina	1995–2006	323	26	8.05	+++	+	++	6
Gimeno, 2005‡ [33]	Madrid, Spain	1986–2003	962	83	9.6	+++	+	++	6
Bertelli, 2005 [54]	Bologna, Italy	1986–2003	721	64	8.8	+++	+	++++	8
Shi, 2003 [47]	Camperdown, Australia	1986–2000	433	19	4.4	++	+	+++	6
Dumortier, 2002 [25]	Lyon, France	1990–2000	468	38	8.1	+++	+	+++	7
Molmenti, 2002 [40]	Dallas, USA	1984–1999	1546	85	5.5	++++	+	+++	8
Yerdel, 2000 [14]	Birmingham, UK	1987–1996	779	63	8.1	++++	+	+++	8
Figueras, 1997 [28]	Barcelona, Spain	1993–1996	119	14	11.76	+++	+	++	6
Lerut, 1997 [37]	Brussels, Belgium	1984–1995	326	38	11.6	++++	+	+++	8
Gayowski, 1996 [31]	Pittsburgh, USA	1989–1994	99	23	23.2	+++	+	++	6

LT, liver transplant; PVT, portal vein thrombosis.

This table reports the prevalence of PVT in liver transplant candidates' cohorts as well as the quality analysis of included studies, according to Newcaste–Ottawa scale.

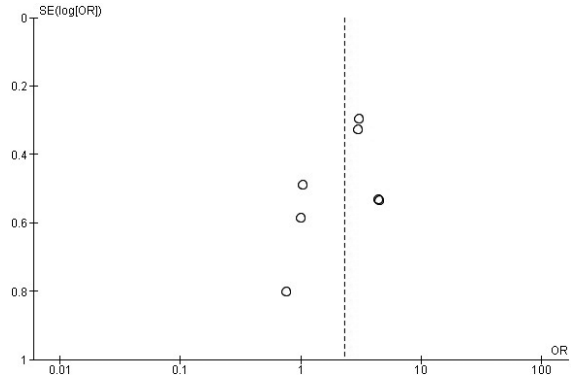

Figure 2 Thirty-days mortality funnel plot. Funnel plot (30 days mortality) shows no significant publication bias among included studies.

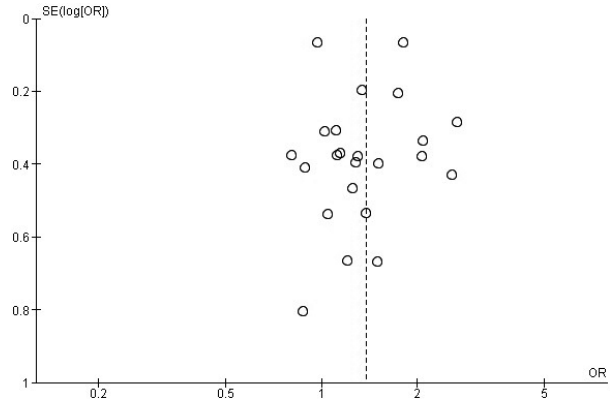

Figure 3 One-year mortality funnel plot. Funnel plot (1 year mortality) shows no significant publication bias among included studies.

Unfortunately, mortality could not be analyzed by surgical technique, and the time of death was unavailable in most studies.

Discussion

In the past, PVT was considered as an absolute contraindication to LT because of the technical difficulties it entailed [62,63]. More recently, surgical techniques like thrombectomy, and the use of venous jump grafts and PV tributaries have overcome many of the technical obstacles involved [49]. The impact of PVT on morbidity and mortality after LT remains unclear, however, since published findings have been controversial.

In their single-center experience, Yerdel *et al.* [14] found a higher in-hospital mortality for patients with PVT than for matched controls (30% vs. 12.4%; $P < 0.01$), and then Englesbe *et al.* [27] confirmed a significantly lower 30-day survival after LT among patients with PVT (17.7% vs. 4.4%, $P = 0.07$). Together with single-center studies, registry studies have also confirmed this higher mortality among patients with PVT [10]. On the other hand, PVT did not emerge as a significant risk factor for early graft loss in the study by Angelico *et al.* [64] on data from an Italian multicenter LT cohort ("Liver match").

In the present meta-analysis, in seven studies on 490 LT recipients, the 30-day pooled mortality rate was higher for patients with PVT (13%) than for other patients (7%), and the presence of PVT was associated with a less marked, but still significant increase in 1-year mortality too (13.5% vs. 9.9%).

Quality assessment of nonrandomized studies is an important factor in a thorough meta-analysis of such studies, as poor-quality studies can lead to a distortion of the summary effect being estimated. In our analysis, the mean quality on the Newcastle–Ottawa scale was 7.1, confirming that our study selection process was appropriate, the resulting groups were comparable, and the reliability of the outcome was adequate. The impact of any significant selection bias was excluded, as shown by the funnel plots.

In our analysis, complete PVT was responsible for the higher mortality, as Englesbe *et al.* [27] had shown in a study on registry data that included 47 patients with complete PVT who underwent LT. Although only 10 studies provided details on patient survival by grade of PVT grade, a higher mortality (ranging from 8.6% to 27%) was associated with reportedly occlusive PVT (including both patients with complete PVT of the main trunk, and patients with diffuse PVT extending to the SMV), with no significant data heterogeneity ($I = 0.46\%$). Complete obstruction of the PV and/or extension to the SMV can be treated by means of various venous jump graft reconstructions or PV arterialization [11]. Nonanatomical solutions, particularly portocaval hemitransposition (PCHT), do not cure portal hypertension, which complicates patients' postoperative course, with a negative fallout on their quality of life in approximately 50% of patients [45,59,65]. Among 49 patients who underwent portocaval hemitransposition in the published cohorts [30,45,57–60,66], 20% had episodes of variceal bleeding, 58% had persistent ascites, and 26% developed renal dysfunction after LT. In the most recent series [58,65], the 1-year pooled mortality rate was 40% (6/16). Improving technical experience in portal thrombectomy, and better solutions for graft reperfusion [40,45,67] may reduce the post-transplant mortality to less than 20% in patients with PVT extending to the SMV [58–60]. Patients should therefore not be refused LT, as long as their surgical

Table 2. Prevalence of portal vein thrombosis in patients undergoing liver transplantation.

Author, year (reference)	Center	Period	Total LT	LT in patients with PVT	Prevalence (%)
Karvellas, 2017 [56]	Alberta, Canada	2002–2012	505	61	14
Gao, 2016 [55]	China Liver transplant registry	1993–2013	18 856	1697	8.5
Ghabril, 2016 [32]	OPTN, USA	2002–2013	50 393	3321	6.6
Hibi, 2014 [34]	Miami, USA	1998–2009	1379	174	12.6
D'Amico, 2013 [53]	Modena, Italy	2000–2010	447	51	11.4
Ravaioli, 2011 [45]	Bologna, Italy	1998–2008	889	91	10.2
Sharma, 2010 [46]	Rochester, USA	1995–2007	1171	78	6.6
Englesbe, 2010 [27]	Ann Arbor, USA	1995–2007	574	30	4.9
Ramos, 2010 [44]	San Paulo, Brazil	1991–2009	419	27	6.4
Suàrez, 2010 [50]	Seville, Spain	1991–2009	670	48	7.1
Shi, 2010 [48]	Chengdu, China	1999–2007	404	48	11.9
Doenecke, 2010 [23]	Regensburg, Germany	2004–2007	193	24	12.4
Tao, 2009 [51]	Shangai, China	2002–2006	465	42	9
Wu, 2009 [52]	Shenyang, China	1995–2007	194	24	12.3
Gao, 2009 [30]	Beijing, China	2004–2008	308	46	14.9
Pan, 2009 [43]	Tianjin, China	1998–2007	2614	253	10.1
Duffy, 2009 [24]	Los Angeles, USA	1984–2007	4234	216	5.1
Nikitin, 2009 [41]	Dallas, USA	1985–2006	2370	141	5.9
Cho, 2008 [22]	Seoul, Korea	2000–2004	133	22	16.5
Arcadipane, 2008 [19]	Palermo, Italy	1999–2007	366	33	9
Lendoire, 2007 [9]	Buenos Aires, Argentina	1995–2006	323	26	8
Lladò, 2007 [38]	Barcelona, Spain	1999–2004	366	42	11.5
Egawa, 2006 [26]	Kyoto, Japan	1996–2004	404	39	9.7
Bertelli, 2005 [54]	Bologna, Italy	1986–2003	721	64	8.8
Gimeno, 2005 [33]	Madrid, Spain	1986–2003	962	83	9.6
Francoz, 2005 [29]	Clichy, France	1996–2001	206	32	15.53
Orlando, 2004 [42]	Rome, Italy	1992–2003	237	27	11.4
Robles, 2004 [17]	Murcia, Spain	1988–2001	455	40	8.79
Shi, 2003 [47]	Camperdown, Australia	1986–2000	433	19	4.4
Dumortier, 2002 [25]	Lyon, France	1990–2000	468	38	8.1
Molmenti, 2002 [40]	Dallas, USA	1984–1999	1564	85	5.5
Manzanet, 2001 [39]	Valencia, Spain	1991–1998	415	62	15.9
Brancatelli, 2001 [20]	Pittsburgh, USA	1997–2000	338	39	10.3
Yerdel, 2000 [14]	Birmingham, UK	1987–1996	779	63	8.1
Figueras, 1997 [28]	Barcelona, Spain	1993–1996	119	14	11.76
Karatzas, 1997 [35]	Miami, USA	1994-1996	343	26	7.5
Lerut, 1997 [37]	Brussels, Belgium	1984–1995	326	38	11.6
Gayowski, 1996 [31]	Pittsburgh, USA	1989–1994	99	23	23.2
Davidson, 1994 [61]	London, UK	1988–1992	140	14	10
Cherqui, 1993 [21]	Cretil, France	1989–1992	70	11	16
Langnas, 1992 [36]	Omaha, USA	1985–1991	367	16	3.81
Nonami, 1992 [1]	Pittsburgh, USA	1989–1990	768	110	14.3
Stieber, 1991 [49]	Pittsburgh, USA	1984–1990	1585	34	2.1

LT, liver transplantation; OPTN, organ procurement and transplant network database; PVT, portal vein thrombosis.
This tables reports the prevalence of PVT in liver transplant candidates cohorts.

risk (dictated by additional comorbidities) is acceptable and an adequate transplant benefit can be expected. In the absence of an alternative, effective therapy, candidates for LT with porto-mesenteric thrombosis nonetheless carry a higher mortality risk while on the waiting list [68]. To sum up, although it is true that mortality after LT is very high in patients with grade 4 PVT, an appropriate transplant benefit may still be achieved in selected cases. Unfortunately, no specific studies have been conducted as yet to answer this crucial question because the only study on transplant benefit that analyzed PVT did not distinguish cases according to their extension [27]. Since the technical complexity of restoring portal graft flow in such cases demands a particular

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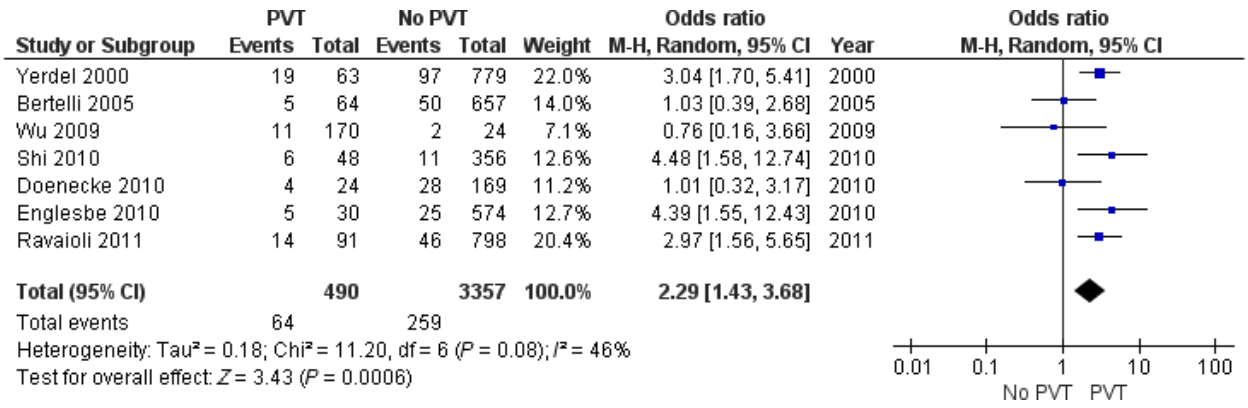

Figure 4 Forest plot 30-days mortality. PVT, portal vein thrombosis. Forest plot shows there was a significant increase in short-term (30-days) mortality in liver transplant recipients with portal vein thrombosis when compared to recipients without portal vein thrombosis.

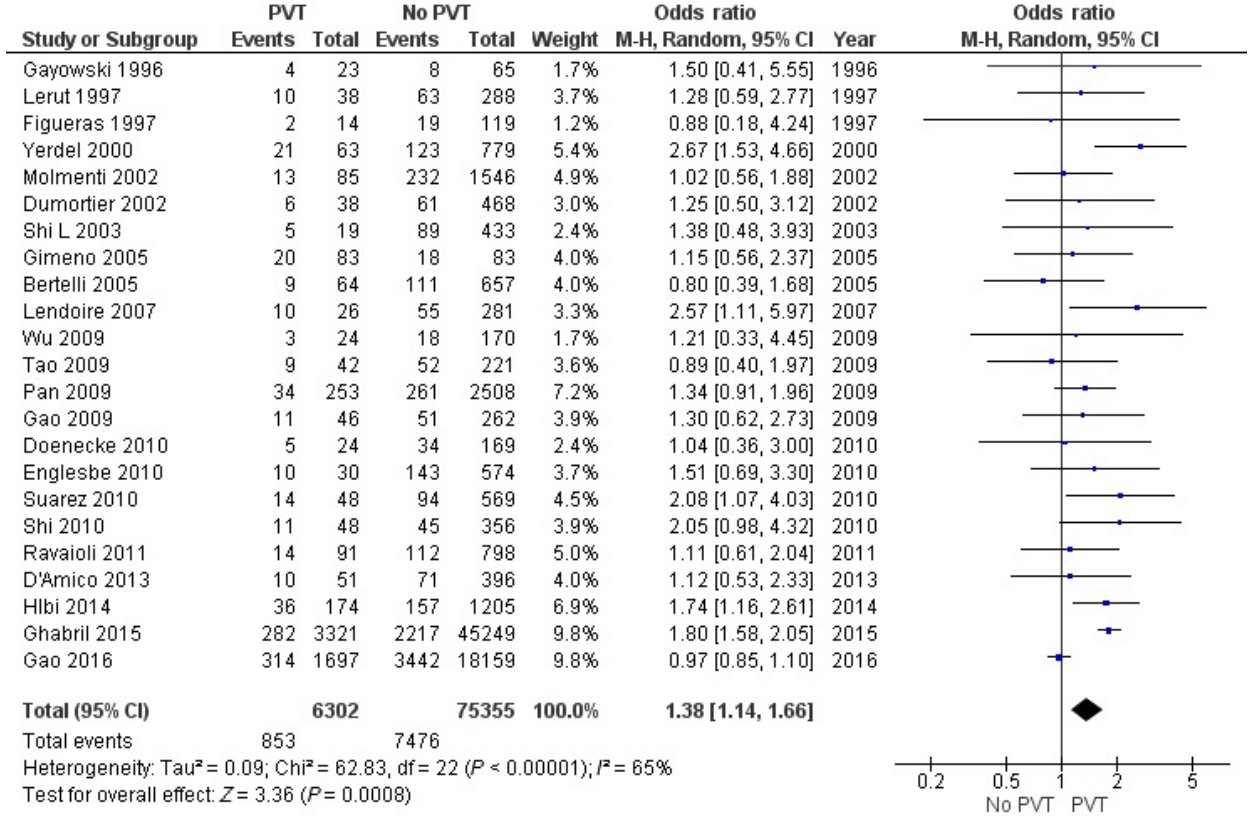

Figure 5 Forest plot 1 year mortality. PVT, portal vein thrombosis. Forest plot shows there was a significant increase in 1-year mortality in liver transplant recipients with portal vein thrombosis when compared to recipients without portal vein thrombosis.

expertise, the patients involved should be addressed to centers acknowledged for their specific surgical experience [67]. This is on the understanding that PVT should be treated in patients awaiting LT, as also stated in the European Association for the Study of the Liver Guidelines for the management of vascular liver diseases [69]. The aim of anticoagulation therapy should be to restore vessel patency or reduce the extent of thrombosis to enable an anatomical reconstruction. Long-term anticoagulation therapy, up until LT, is to be recommended because the rate of recurrence of PVT after its withdrawal is high [70]. When anticoagulation therapy is contraindicated, or fails, a radiological approach could be attempted [71]. In a recent study by Salem *et al.* [72], repermeation of the thrombosed PV was achieved in 43 of 44 patients by trans-splenic and/

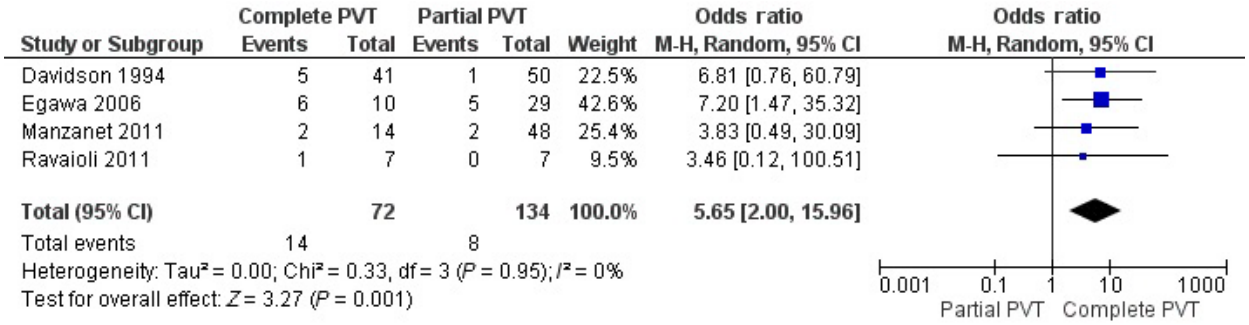

Figure 6 Forest plot 30 day mortality in recipients with partial versus complete PVT. PVT, portal vein thrombosis. Forest plot shows there was a significant increase in short-term (30-days) mortality in liver transplant recipients with complete portal vein thrombosis when compared to recipients with partial portal vein thrombosis.

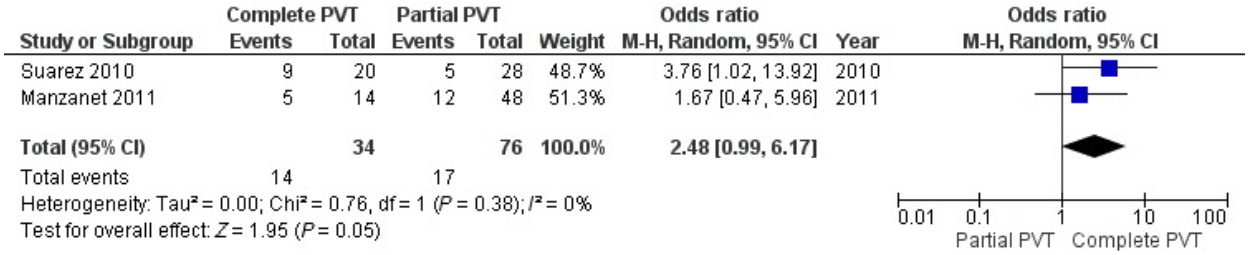

Figure 7 Forest plot 1 year mortality in recipients with partial versus complete PVT. PVT, portal vein thrombosis. Forest plot shows there was a significant increase in short-term (30-days) mortality in liver transplant recipients with complete portal vein thrombosis when compared to recipients with partial portal vein thrombosis, although it was at inferior limit of statistical significance.

or transjugular TIPS placement. Over the last few years, a great deal of progress has been made in the technical management of portal thrombosis during LT, even in cases of extended splanchnic thrombosis. This seems to have had no significant impact in reducing LT recipients' mortality over time, however, especially in patients with grade 4 PVT [45]. It is worth noting that, given the significantly higher short- and medium-term mortality in this subset of patients, the possibility of performing LT in such candidates should be carefully assessed, case by case. Other factors need to be considered too, such as pressure on the waiting list, in order to guarantee the principle of equity in the liver graft allocation process and to avoid futile liver transplants.

The present study has some significant limitations that need to be acknowledged. First, we were unable to include any prospective studies in our meta-analysis. Second, although the mean quality of the studies analyzed was good, many of them did not report important variables regarding liver disease severity, so we only just avoided the potential bias regarding the difference in survival between the groups. Third, in many cases, there was no appropriate description of patients' PVT, based on Yerdel's classification. There was also a shortage of details about the causes of death and how they related to patients' PVT at the time of their LT. The enrollment period was relatively long too, so different transplant policies, and rules for prioritization and inclusion may have unavoidably influenced our findings.

In conclusion, there is a high prevalence of PVT among LT candidates. When complete and extending to the SMV, PVT is associated with less favorable post-LT outcomes in terms of both morbidity and mortality. It is therefore recommended that patients undergo adequate screening while on the waiting list and receive prompt medical or radiological treatment in order to guarantee the patency of their portal vein at the time of their transplant procedure.

Authorship

AZ and KIRC: conducted bibliographic research, and drafted the manuscript. GG and AF: conducted bibliographic research. UC and PB: revised the manuscript. MS: conceived the study, analyzed the literature and revised the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Forest plot 1 year mortality before 2005.

Figure S2. Forest plot 1 year mortality from 2005.

Figure S3. One-year mortality before 2005 funnel plot.

Figure S4. One-year mortality from 2005 funnel plot.

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