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Review article

Grafts from selected deceased donors over 80 years old can safely expand the number of liver transplants: A systematic review and meta-analysis☆

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ABSTRACT

Aim: The aim of this systematic review and meta-analysis was to present the outcome of deceased adult liver transplantation from octogenarian (≥80 years old) donors compared to younger grafts.
Methods: A systematic search was performed on six databases to identify all available original papers that report the outcome of adult recipients who underwent liver transplantation from a deceased octogenarian donor.
Results: Overall, 39,034 liver transplantations from 12 studies were reported with 789 (2.02%) cases receiving grafts from octogenarian donors. Eight studies were included in the meta-analysis. There was no difference regarding the one, three, and five-year graft and patient survival between the recipients of livers <80 years old and octogenarian grafts. There were significantly more episodes of biliary complications in the recipients of octogenarian grafts (34/459; 7.4%) in comparison to the recipients of livers <80 years old (372/37074; 1.0%) (OR 0.53; 95% CI = 0.35–0.81; P 0.004; $I^2 = 0\%$). The incidence of primary non-function, vascular complications and re-transplantation did not differ between groups.
Conclusions: The short- and medium-term graft and patient survival of octogenarian liver transplantation is not inferior compared to the liver transplantation with younger grafts, however with a higher rate of biliary complications.

Contents

Abbreviations: ALD, Alcoholic liver disease; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BC, Biliary complication; CI, Confidence interval; DAA, Direct-acting antiviral agents; DRI, Donor risk index; CIT, Cold ischemia time; HCV, Hepatitis C virus; ICU, Intensive care unit; ITBL, Ischemic-type biliary lesions; LTx, Liver transplantation; MELD, Model for End-Stage Liver Disease; PNF, Primary non-function; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; re-LTx, Liver re-transplantation; RR, Risk ratio; VC, Vascular complication; WIT, Warm ischemia time.

☆ Study type: systematic review and meta-analysis

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1. Introduction

Liver transplantation (LTx) is a life-saving procedure routinely performed in many centres every day. Not all patients with end-stage liver disease can benefit from LTx, primarily due to organ shortage and changes in the recipient population. In the United States, >1700 patients died on the waiting list and >1200 patients were removed from the list due to health deterioration in 2013 [1].

A significant change regarding the age of the liver donors has been observed during the past 20 years, in which liver donors older than 60 years were used as an exception at the beginning of this period [2]. Only 1% of livers were procured from donors older than 60 years in 1989 according to the European Liver Transplant Registry, as compared to 29% in 2009 [3]. Nowadays, liver grafts from donors older than 60 or 70 years are routinely used for transplantation, as their outcomes are comparable to that of younger grafts [4–6].

Although the impact of the donor's age on patient and graft survival after LTx has been previously studied, the results are conflicting [7–12]. Moreover, some cohort studies indicate comparable survival outcomes with a higher rate of complications [13], including re-transplantation [14]. In many studies, it has been emphasized that the donor age alone does not affect the outcome when other risk factors are absent [15–17]. This is because factors related to both the donor and the recipient's outcome hamper any clear conclusions [18]. For example, recipients infected with hepatitis C virus (HCV) have been reported to have the poor outcome associated with being transplanted with an older graft [19–21].

The age cut-off for deceased donors is a subject of discussion. Recently, a systematic review and meta-analysis of LTx using grafts from septuagenarian (≥ 70 years) donors was reported by the Dasari et al. [22] Comparable patient and graft survival, as well as early graft function and complication rates were reported, encouraging the use of these older grafts for transplantation. Furthermore, the livers from donors aged 80 years or older (octogenarian) are used more often, and case reports indicate the successful use of livers from donors older than 90 years [23,24].

The aim of this systematic review and meta-analysis was to determine the outcome of deceased adult LTx with grafts procured from octogenarian (≥ 80 years) donors in comparison with that of younger grafts (< 80 years).

2. Methods

A systematic search was performed to identify all available original papers that report the outcome of adult recipients who underwent LTx with grafts retrieved from deceased octogenarian donors. Reviews, opinion articles, case reports, cases series, letters to editor, and conference papers were excluded from the analysis.

2.1. Criteria used for the review

2.1.1. Inclusion and exclusion criteria

All studies that reported adult patients (≥ 18 years) who underwent primary orthotopic and whole LTx with grafts from brain death donors were included. Studies reporting paediatric LTx, re-transplantations, split LTx, living liver donors LTx, liver donors after circulatory death or paediatric liver donors (donor age < 16 years) were excluded from this review. In cases in which more than one published study from the same centre involving the same patient cohort was used in different studies, only the most recent study was included in this analysis.

2.1.2. Intervention and control

The results of LTx with grafts procured from octogenarian (≥ 80 years) donors where compared with that of younger grafts (< 80 years).

2.1.3. Outcome variables

The primary outcome was one, three and five-year graft and patient survival following LTx. Primary non-function (PNF), vascular (VC) and biliary complications (BC), as well as the liver re-transplantation (re-LTx) rate were investigated as secondary outcomes. PNF was defined as an initial lack of function or very poor function leading to early (usually within seven days) re-transplantation or death. Complications were defined by the studies' authors and consisted the most frequently of hepatic artery or portal vein thrombosis in cases involving VC and bile leakage and/or biliary stricture in cases of BC.

2.2. Search methodology and study identification

2.2.1. Database query

Proper queries were constructed regarding search strings and corresponding terms (Table S1, supporting information). The search was conducted on the 1st of February 2019 and applied to six databases: Embase, Medline Ovid, Web of Science, Cochrane CENTRAL, CINAHL EBSCOhost and Google scholar. The search was limited to English papers without any limitations regarding the year of publication. After removing any duplicate records, the studies (based on title and abstract) were screened separately by

two independent investigators to determine which paper was eligible for further analysis. The third investigator searched for any discrepancies between the first two reviewers. Full-text articles were obtained and investigated to meet the inclusion criteria and at least one outcome variable. The process was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25].

2.2.2. Quality assessment

Two investigators independently assessed the quality of the studies (cohort and case controlled studies) included in the meta-analysis using the Newcastle-Ottawa scale [26] for each study.

2.2.3. Data extraction

Each eligible study was investigated, and the data included the type of the study, year of publication, study design, number of participants, inclusion and exclusion criteria, mean donor age and the outcome variables defined above were extracted.

2.3. Statistical analysis

Outcomes were reported as they were presented in the original articles according to the defined variables. The descriptive statistics included the median and interquartile range for continuous variables and absolute numbers (with the percentage rate) for categorical variables. The meta-analysis was performed using Review Manager Version 5.3 software (RevMan; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) provided by the Cochrane Collaboration [27]. The results were presented as the odds ratio (OR) with a corresponding 95% confidence interval (CI). The term I^2 was used to determine the heterogeneity of the studies. The funnel plots were used to

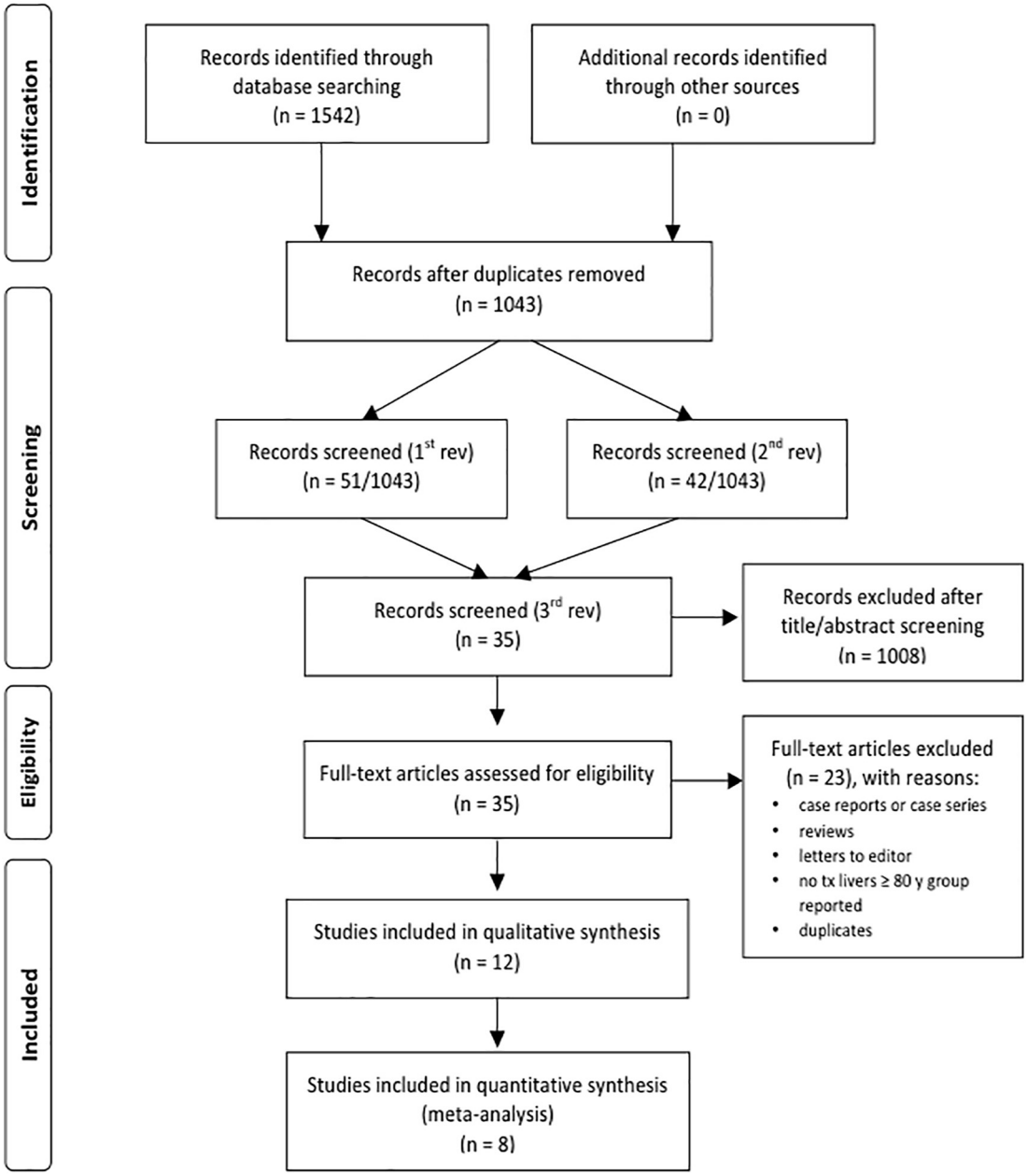


Fig. 1. PRISMA flow chart: selection of articles for review.

evaluate the risk of publication bias. The random-effect model was used for reporting outcomes. A *P*-value below 0.05 was considered to be statistically significant.

3. Results

The literature search identified 1542 records, 12 of which matched the inclusion criteria (Fig. 1). The majority of studies (75%) were published after the year 2010 and there were no randomized controlled studies among them. There were nine cohort studies and two case-controlled studies (Table 1). Overall, 39,034 liver transplantations were reported with 789 (2.02%) receiving grafts from octogenarian donors. Eight studies were included in the meta-analysis as they reported at least one outcome variable and the data regarding the control group (patients following a liver transplantation from donors younger than 80 years old) were possible to extract as comparative studies (Table S2, supporting information). Three cohort studies [28–30] as well as one case control study [31] were excluded from the meta-analysis since data regarding the control group were not available in these studies.

3.1. Donor and recipient characteristics

Different donor and recipient features were analysed when comparing younger (< 80 years) and older (≥ 80 years) liver graft recipients in the reviewed studies. There were no differences between the donors and recipients regarding gender, body mass index (BMI), cause of donor death, donor biochemical parameters (with some exceptions), liver steatosis (if it was reported), recipient age or liver disease reported in three studies [32–34].

Gajate et al. [33] reported a higher sodium serum concentration (147 vs. 142 mEq/L; P 0.001) and longer intensive care unit (ICU) length of stay (48 vs. 29 h; P 0.001) in the younger donors compared to the older donors, respectively. In this study, the younger liver recipients presented slightly more severe medical conditions expressed by the Model for End-Stage Liver Disease (MELD) score in comparison to older liver recipients (Table 2). Moreover, Diaz et al. [32] presented a longer ICU length of stay (2.3 vs. 1.6 days; P 0.01), higher levels of aspartate aminotransferase (AST) (64 vs. 32 U/L; P 0.01) and higher levels of alanine aminotransferase (ALT) (55 vs. 21 U/L; P 0.01) in younger donors compared to older donors, respectively. Recipients of older livers in this study were older and had a lower MELD compared to the recipients of younger livers; however, these differences were not significant. Roullet et al. [35] compared six groups composed according to donor age. They found that the two oldest donor groups had lower transaminase levels, stayed a shorter length of time in the ICU and most often died of a stroke. Older donors also presented with a higher donor risk index (DRI) calculated according to the model proposed by Feng et al. [36], in which donor age is one of the components (2.5 in the oldest group vs. 1.3 in the youngest group; P 0.001). Montenevo et al. [37] studied four age cohorts according to donor age. There were more female donors and recipients in the older cohorts. Moreover, the recipients of younger livers were more likely to have a higher MELD score and were younger compared to the recipients of older livers. Ghinolfi et al. [38] also found more females lower transaminase levels and sodium concentrations among the octogenarian donors. The recipients of the octogenarian livers were older, had a lower MELD score and a hepatocellular carcinoma lesion presented more frequently in the native liver. According to the data presented by Cescon et al. [39], similar trends were observed. Among the octogenarian donors, there were more females, a shorter length of stay in the ICU and lower levels of ALT. The recipients of older livers more frequently presented with a MELD ≥25.

3.2. Perioperative factors

There were no differences regarding the length of surgery, blood loss, cold (CIT) or warm (WIT) ischemic time in four studies [29,33,34,39]. The data presented by Diaz et al. [32] reported significantly shorter CIT (347 vs. 365 min; P 0.04) and longer WIT (58 vs. 53 min; P 0.03) for older livers compared to younger livers. Zapletal et al. [40] demonstrated no differences regarding CIT, a longer surgery time for LTx from donors <80 years old (5.3 vs. 4.2 h) and increased blood loss (as assessed by the need for blood product transfusion) in comparison to octogenarian donor livers.

3.3. Length of posttransplant ICU and hospital stay

There were no significant differences regarding the length of ICU and/or hospital stay reported in seven studies (Table 3) [28,31–34,38,40].

3.4. Meta-analysis

3.4.1. Graft survival

Five studies included in the meta-analysis reported one-year graft survival [32,33,35,38,40], four studies reported three-year [32,34,38,39] and five-year graft survival [32,35,38,39]. There were no differences regarding the one-year (86.2% vs. 84.4%; OR 1.28; 95% CI = 0.68–2.39; P 0.45; $I^2 = 27\%$), three-year (61.8% vs. 77.1%; OR 0.71; 95% CI = 0.15–3.32; P 0.66; $I^2 = 93\%$) and five-year (72.5% vs. 75.7%; OR 0.92; 95% CI = 0.38–2.26; P 0.86; $I^2 = 74\%$) graft survival between the recipients of livers aged <80 years old and the recipients of octogenarian grafts, respectively (Fig. 2A, B and C).

Table 1
Characteristics of the included studies.[a]

Reference	Country	Studied period	Study type	Number of cases	Number of cases ≥ 80 y	Number of controls[a]	Included to meta-analysis	Median follow-up (months)
Cascales-Campos 2018	Spain	2007–2015	cohort	319	36	283	No	36 (24–120)
Gajate 2018	Spain	2011–2015	cohort	177	38	139	Yes	N/A
Diaz 2017	Spain	2006–2015	case control	36	12	24	Yes	22 (6–108)
Roullet 2017	France	2005–2014	cohort	380	27	353[a]	Yes	43 (24–78)
Jimenez-Romero 2017	Spain	1996–2015	cohort	153	51	102 (≤ 65 y)	No	N/A
Montenovo 2017	USA	2002–2012	cohort	35,886	283	35603[a]	Yes	N/A
Biancofiore 2017	Italy	2001–2014	cohort	346	167	179 (< 40 y)	No	N/A
Rabelo 2016	Spain	2008–2014	cohort	212	14	198[a]	Yes	N/A
Ghinolfi 2014	Italy	2001–2010	cohort	842	85	757[a]	Yes	54 (12−132)
Cescon 2008	Italy	1998–2006	cohort	553	41	512[a]	Yes	39.3 (0–95)
Zapletal 2005	Germany	2002–2004	cohort	40	5	35	Yes	N/A
Nardo 2004	Italy	1998–2003	case control	90	30	60 (< 40 y)	No	30.8 (3.2–52)

N/A – not available.
[a] in studies in which octogenarian liver transplants were compared to different age group cohorts, the control group was created by totalling all of the groups defined with a donor age younger than 80 years old.

Table 2
Donor and recipient characteristics.[a]

Reference	Number of cases	Number of cases		Mean/median donor age		Mean/median recipient age		Mean/median MELD	
		≥ 80 y	< 80 y[a]	≥ 80 y	< 80 y[a]	≥ 80 y	< 80 y[a]	≥ 80 y	< 80 y[a]
Cascales-Campos 2018	319	36	283 (< 65 y)	82.3 ± 2.4	47.5 ± 13.3	59.2 ± 5.7	52.1 ± 10.9	9 (3–28)	15 (1–35)
Gajate 2018	177	38	139	82.1 ± 1.9	59.4 ± 16.9	55.7 ± 7.0	52.3 ± 9.5	16.1 ± 7.9	18.7 ± 9.1
Diaz 2017	36	12	24	82.7 ± 2.7	55.6 ± 14.4	59.5 ± 4.8	56.3 ± 10.1	12.9 ± 4.3	16 ± 9.1
Roullet 2017	380	27	353[a]	82 (80–85)	N/A	57 (53–62)	N/A	13 (9–17)	N/A
Jimenez-Romero 2017	153	51	102 (≤ 65 y)	83.5 ± 2.8	46.9 ± 15.0	58.0 ± 8.7	52.6 ± 11.5	14.5 ± 6.5	14.9 ± 5.5
Montenovo 2017	35,886	283	35603[a]	82 ± 2.4	N/A	59 ± 9.0	N/A	17 ± 3	N/A
Biancofiore 2017	346	167	179(< 40 y)	83 (80–92)	27 (18–39)	57 (52–61)	46 (38–53)	11 (9–15)	13 (10–17)
Rabelo 2016	212	14	198[a]	N/A	N/A	51.79	N/A	18	N/A
Ghinolfi 2014	842	85	757[a]	N/A	N/A	56.3 ± 0.8	N/A	12.2 ± 0.5	N/A
Cescon 2008	553	41	512[a]	N/A	N/A	52.5 ± 10	N/A	19.5 ± 8.5	N/A
Zapletal 2005	40	5	35	N/A (80–83)	N/A	52 ± 8	52 ± 10	13.6 ± 1.7	20.2 ± 8.5
Nardo 2004	90	30	60 (< 40 y)	82.3 ± 3.1	27.6 ± 7.94	52.5 ± 9.4	46.7 ± 10.5	N/A	N/A

N/A – not available.
[a] In studies, in which octogenarian liver transplants were compared to different age group cohorts, the control group was created by totalling all of the groups defined with a donor age younger than 80 years old.

3.4.2. Patient survival

Three studies that were included in the meta-analysis reported three-year patient survival [32,38,39], four studies reported one-year [32,35,38,40] and four studies reported five-year patient survival [32,35,38,39]. There were no differences regarding the one-year (88.7% vs. 88.4%; OR 1.18; 95% CI = 0.53–2.63; P 0.68; I^2 = 18%), three-year (81.1% vs. 80.4%; OR 1.02; 95% CI = 0.56–1.86; P 0.94; I^2 = 27%) and five-year (76.4% vs. 82.4%; OR 0.61; 95% CI = 0.27–1.40; P 0.24; I^2 = 60%) patient survival between the recipients of livers aged <80 years old and recipients of octogenarian grafts, respectively (Fig. 2D, E and F).

3.4.3. Primary non-function

Seven studies [32,33,35,37–40] involving a total of 37,914 patients that were included in the meta-analysis described the rate of PNF (Fig. 3A). There was no significant difference in the rate of PNF between the recipients of octogenarian grafts (3/491; 0.6%) and recipients of livers aged <80 years old (216/37423; 0.6%) (OR 0.73; 95% CI = 0.26–2.07; P 0.55; I^2 = 0%).

3.4.4. Vascular complications

VC data could be extracted from five studies [32–35,37] included to the meta-analysis (out of nine) involving 36,691 patients (Fig. 3B). There was no significant difference in the VC rate between the recipients of octogenarian grafts (4/374; 1.1%) and the recipients of livers aged <80 years old (353/36317; 1.0%) (OR 1.45; 95% CI = 0.54–3.88; P 0.46; I^2 = 0%).

3.4.5. Biliary complications

The BC data of 37,533 patients from six studies [32–35,37,38] were included in the meta-analysis (Fig. 3C). There were significantly more episodes of BC among the recipients of octogenarian grafts (34/459; 7.4%) compared to the recipients of livers <80 years old (372/37074; 1.0%) (OR 0.53; 95% CI = 0.35–0.81; P 0.004; I^2 = 0%).

3.4.6. Re-transplantation

The re-transplantation rate was reported in 1191 patients in six out of eight studies [32–35,37,40] that were included in the meta-analysis (Fig. 3D). The recipients of octogenarian livers were found to have the same probability of being re-transplanted (9/379; 2.4%) as the

Table 3
Results of liver transplantation between groups.

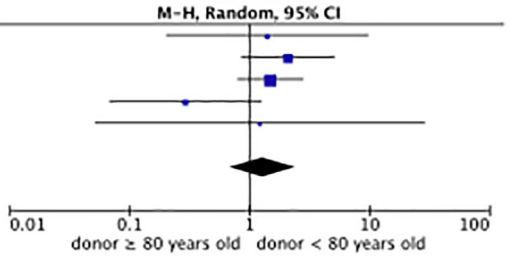
Reference	ICU-stay (days)		Hospital stay (days)		Graft survival (%)		Patient survival (%)	
	≥ 80 y	< 80 y[a]	≥ 80 y	< 80 y[a]	≥ 80 y	< 80 y[a]	≥ 80 y	< 80 y[a]
Cascales-Campos 2018	9.6 ± 24.1	6.3 ± 12.9	26.9 ± 11.6	28.6 ± 19.4	1 y – 77% 2 y – 72% 3 y – 62%	1 y – 79% 2 y – 73% 3 y – 65%	1 y – 86% 2 y – 82% 3 y – 75%	1 y – 82% 2 y – 76% 3 y – 72%
Gajate 2018	3 (3–5)	3 (2–5)	17.5 (12−31)	18 (14–28)	1 y – 76	1 y – 87	N/A	N/A
Diaz 2017	5.7 ± 6.3	4.6 ± 3.5	18.7 ± 16.5	17.25 ± 12.1	1 y – 83.3 3 y – 54.7 5 y – 27.3	1 y – 87.5 3 y – 87.5 5 y – 70.0	1 y – 91.7 3 y – 80.2 5 y – 80.2	1 y – 95.8 3 y – 79.9 5 y – 79.9
Roullet 2017	N/A	N/A	N/A	N/A	1 y – 92.6 5 y – 84.3 10 y – 84.3	N/A	1 y – 92.6 5 y – 92.6 10 y – 92.6	N/A
Jimenez-Romero 2017	7.3 ± 8.5[b]	5.1 ± 5.1[b]	24.3 ± 17.6	21.9 ± 17.6	1 y – 84.3 3 y – 79.4 5 y – 64.2	1 y – 84.3 3 y – 83.1 5 y – 74.2	1 y – 88.2 3 y – 84.1 5 y – 66.4	1 y – 87.3 3 y – 84 5 y – 75.2
Montenovo 2017	N/A	N/A	N/A	N/A	N/A[c]	N/A[c]	N/A[c]	N/A[c]
Biancofiore 2017	3 (2–4)	3 (2–5)	15 (12–24)	14 (11−20)	1 y – 85.9 3 y – 72.1 5 y – 71.1[b]	1 y – 94.4 3 y – 83.4 5 y – 81.6[b]	N/A	N/A
Rabelo 2016	7.07	N/A	N/A	N/A	3 y – 40	N/A	3 y – 40	N/A
Ghinolfi 2014	2 (1−13)	N/A	20.7 ± 1.9	N/A	1 y – 84.7 3 y – 77.1 5 y – 77.1	N/A	1 y – 85.9 3 y – 78.2 5 y – 78.2	N/A
Cescon 2008	N/A	N/A	N/A	N/A	3 y – 81 5 y – 81	N/A	3 y – 86 5 y – 86	N/A
Zapletal 2005	2.4 ± 1.1	5 ± 6	22 ± 7	31 ± 17	1 y – 100	1 y – 94.3	1 y – 100	1 y – 94.3
Nardo 2004	4.7 ± 2.3	5.1 ± 7.4	19 ± 5.5	21.9 ± 14.3	3 m – 96.7 6 m – 90	3 m – 90 6 m – 90	3 m – 100 6 m – 93.3	3 m – 96.7 6 m – 96.7

ICU – intensive care unit.
PNF – primary non-function.
re-LTx – liver re-transplantation.
N/A – not available.
[a] in studies, in which octogenarian liver transplants were compared to different age group cohorts, the control group was created by summing up all groups defined with the donor age younger than 80 years old.
[b] Statistically significant difference (p 0.05).
[c] Graft and patient survival presented as Kaplan-Meier graph without the possibility to extract numbers.

(a)

Study or Subgroup	donor < 80 years old Events	Total	donor ≥ 80 years old Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Diaz 2017	21	24	10	12	9.2%	1.40 [0.20, 9.75]
Gajate 2018	121	139	29	38	29.7%	2.09 [0.85, 5.12]
Ghinolfi 2014	675	757	72	85	42.6%	1.49 [0.79, 2.80]
Roullet 2017	277	353	25	27	14.8%	0.29 [0.07, 1.26]
Zapletal 2005	33	35	5	5	3.7%	1.22 [0.05, 28.93]
Total (95% CI)		**1308**		**167**	**100.0%**	**1.28 [0.68, 2.39]**
Total events	1127		141			

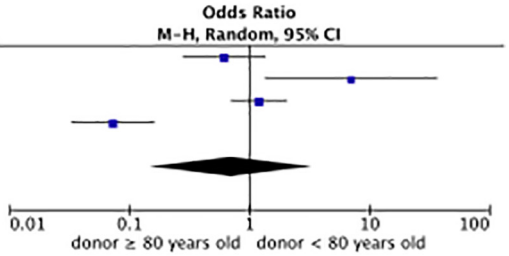
Heterogeneity: Tau² = 0.14; Chi² = 5.46, df = 4 (P = 0.24); I² = 27%
Test for overall effect: Z = 0.76 (P = 0.45)



(b)

Study or Subgroup	donor < 80 years old Events	Total	donor ≥ 80 years old Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Cescon 2008	367	512	33	41	26.0%	0.61 [0.28, 1.36]
Diaz 2017	21	24	6	12	21.1%	7.00 [1.34, 36.69]
Ghinolfi 2014	610	757	66	85	27.0%	1.19 [0.70, 2.05]
Rabelo 2016	118	512	33	41	25.9%	0.07 [0.03, 0.16]
Total (95% CI)		**1805**		**179**	**100.0%**	**0.71 [0.15, 3.32]**
Total events	1116		138			

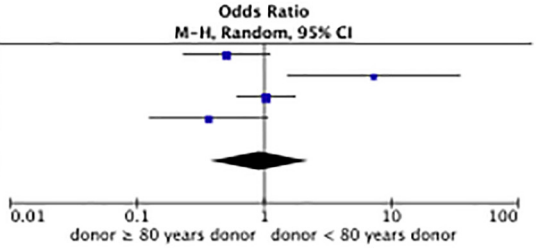
Heterogeneity: Tau² = 2.23; Chi² = 41.68, df = 3 (P < 0.00001); I² = 93%
Test for overall effect: Z = 0.44 (P = 0.66)



(c)

Study or Subgroup	donor < 80 years old Events	Total	donor ≥ 80 years old Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Cescon 2008	346	512	33	41	27.9%	0.51 [0.23, 1.12]
Diaz 2017	17	24	3	12	17.0%	7.29 [1.51, 35.21]
Ghinolfi 2014	592	757	66	85	31.7%	1.03 [0.60, 1.77]
Roullet 2017	239	353	23	27	23.5%	0.36 [0.12, 1.08]
Total (95% CI)		**1646**		**165**	**100.0%**	**0.92 [0.38, 2.26]**
Total events	1194		125			

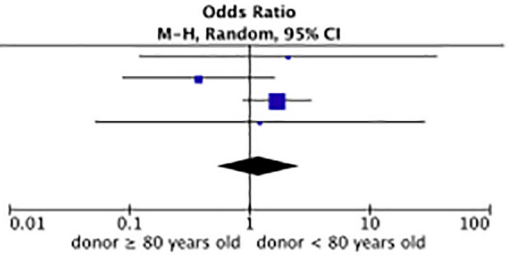
Heterogeneity: Tau² = 0.58; Chi² = 11.65, df = 3 (P = 0.009); I² = 74%
Test for overall effect: Z = 0.17 (P = 0.86)



(d)

Study or Subgroup	donor < 80 years old Events	Total	donor ≥ 80 years old Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Diaz 2017	23	24	11	12	7.3%	2.09 [0.12, 36.64]
Ghinolfi 2014	291	353	25	27	23.4%	0.38 [0.09, 1.63]
Roullet 2017	690	757	73	85	63.3%	1.69 [0.87, 3.28]
Zapletal 2005	33	35	5	5	6.0%	1.22 [0.05, 28.93]
Total (95% CI)		**1169**		**129**	**100.0%**	**1.18 [0.53, 2.63]**
Total events	1037		114			

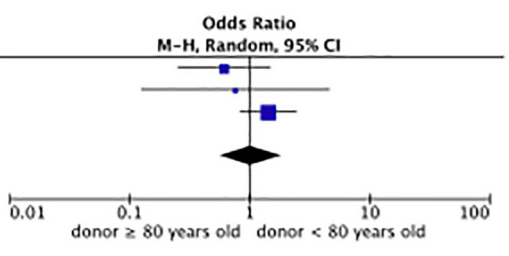
Heterogeneity: Tau² = 0.15; Chi² = 3.65, df = 3 (P = 0.30); I² = 18%
Test for overall effect: Z = 0.42 (P = 0.68)



(e)

Study or Subgroup	donor < 80 years old Events	Total	donor ≥ 80 years old Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Cescon 2008	400	512	35	41	32.1%	0.61 [0.25, 1.49]
Diaz 2017	19	24	10	12	9.9%	0.76 [0.12, 4.64]
Ghinolfi 2014	630	757	66	85	58.0%	1.43 [0.83, 2.46]
Total (95% CI)		**1293**		**138**	**100.0%**	**1.02 [0.56, 1.86]**
Total events	1049		111			

Heterogeneity: Tau² = 0.08; Chi² = 2.73, df = 2 (P = 0.26); I² = 27%
Test for overall effect: Z = 0.07 (P = 0.94)



(f)

Study or Subgroup	donor < 80 years old Events	Total	donor ≥ 80 years old Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Cescon 2008	377	512	35	41	29.5%	0.48 [0.20, 1.16]
Diaz 2017	19	24	10	12	14.2%	0.76 [0.12, 4.64]
Ghinolfi 2014	612	757	66	85	37.6%	1.22 [0.71, 2.09]
Roullet 2017	250	353	25	27	18.7%	0.19 [0.05, 0.83]
Total (95% CI)		**1646**		**165**	**100.0%**	**0.61 [0.27, 1.40]**
Total events	1258		136			

Heterogeneity: Tau² = 0.39; Chi² = 7.49, df = 3 (P = 0.06); I² = 60%
Test for overall effect: Z = 1.16 (P = 0.24)

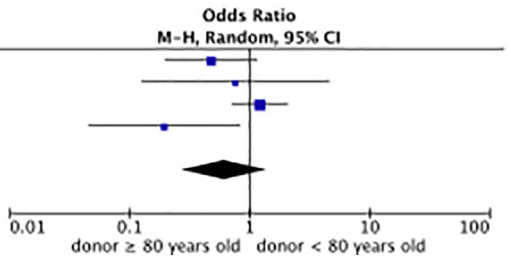


Fig. 2. Comparison of graft survival: one year (A), three years (B) and five years (C) and patient survival: one year (D), three years (E) and five years (F) using grafts <80 years old and ≥ 80 years old.

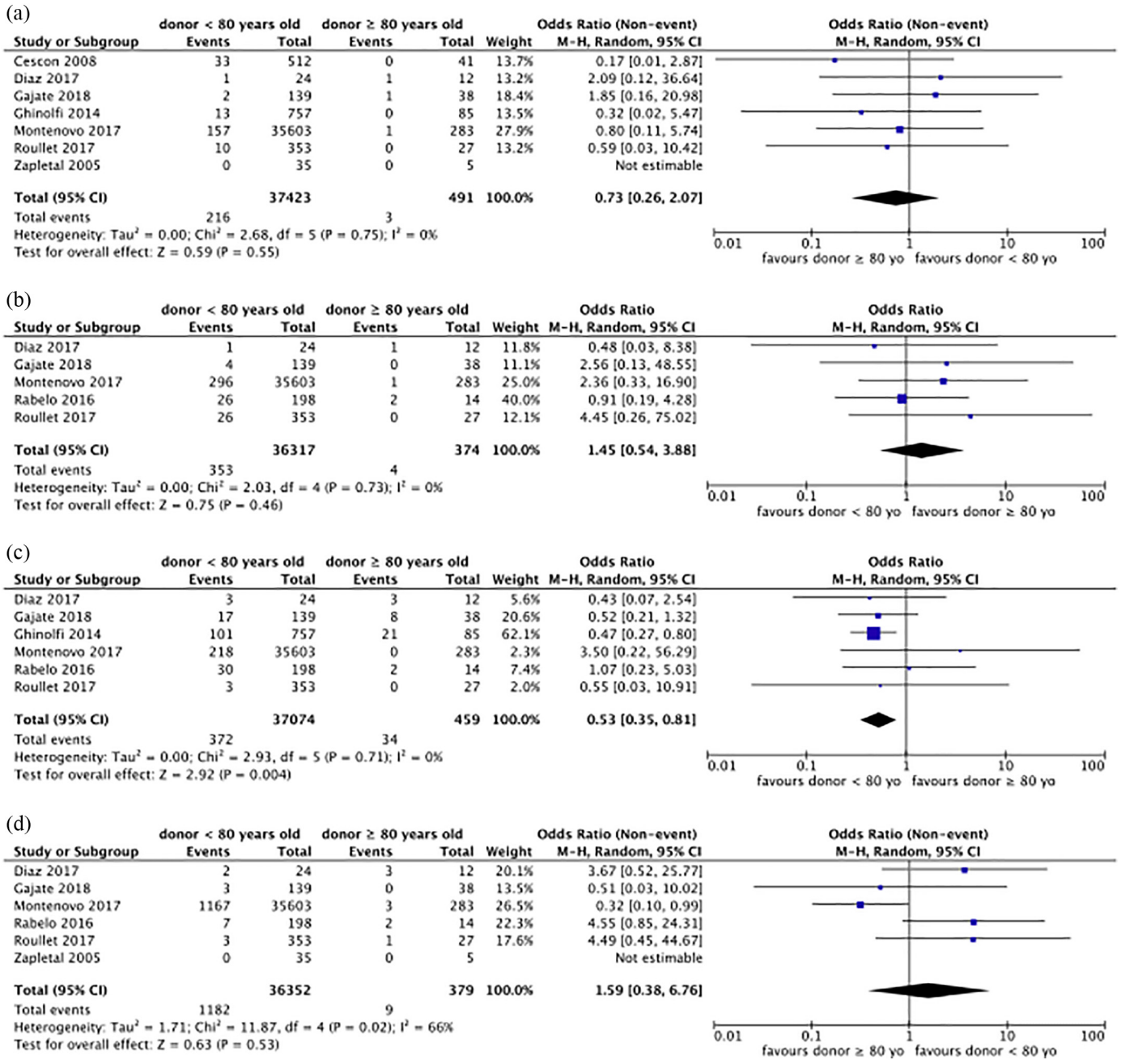


Fig. 3. Comparison of primary non-function (A), vascular complications (B), biliary complications (C) and liver re-transplantations (D) using grafts <80 years old and ≥ 80 years old.

recipients of livers <80 years old (1182/36352; 3.2%) (OR 1.59; 95% CI = 0.38–6.76; P 0.53; $I^2 = 66\%$).

3.5. Meta-analysis of cohort studies

To exclude the bias regards the fact that there were seven cohort studies and one case-control study included to the meta-analysis, the meta-analysis of seven studies has been done and the results did not differ from those presented above.

3.6. Quality assessment

The quality of studies included in the meta-analysis was assessed using the Newcastle-Ottawa scale. The quality was assessed and reported to be moderate (Table 4).

3.7. HCV recipient sub-analysis

A sub-analysis of HCV recipients was performed for eight studies included in this review [28–31,33,38–40]. In one study, non-significant differences were found regarding graft survival between younger graft (<80 years old) and older graft (≥ 80 years old) HCV-positive recipients [33]. Cascales-Campos et al. did not present significant differences in HCV histological recurrence rate in the graft between younger graft (< 65 years old) and older graft (≥ 80 years old) among HCV-positive patients [30].

Jimenez-Romero et al. [29] reported similar one, three and five-year graft survival of younger livers (≤ 65 years old) compared to older livers (≥ 80 years). However, when the patients with HCV cirrhosis were excluded from the analysis, a non-significant improvement in graft survival of older livers was observed (84.9%, 84.9% and 73.8% vs. 85.4%, 85.4% and 76.5% for one, three and five-year graft survival of younger

Table 4
Quality assessment of studies included to the meta-analysis according to Newcastle-Ottawa scale.

Reference	Quality points by outcome								Sum
Case control studies									
	Selection				Comparability	Exposure			
Diaz 2017	1	1	0	1	2	1	1	1	8/9
Cohort studies									
	Selection				Comparability	Outcome			
Gajate 2018	1	0	1	1	2	1	0	0	6/9
Roullet 2017	1	0	1	1	1	1	1	0	6/9
Montenovo 2017	1	0	1	1	1	1	0	0	5/9
Rabelo 2016	1	0	1	1	1	1	0	0	5/9
Ghinolfi 2014	1	0	1	1	1	1	1	0	6/9
Cescon 2008	1	0	1	1	1	1	1	0	6/9
Zapletal 2005	1	0	1	1	2	1	0	0	6/9

and older livers respectively; P 0.41). Using multivariable analyses, Biancofiore et al. [28] found that HCV positivity was a risk factor for prolonged hospitalisation (> 30 days) (OR 2.4; 95% CI = 1.1–5.2; P 0.02) and severe complications (OR 2.0; 95% CI = 1.2–3.2; P 0.01). Moreover, HCV-positive recipients who received octogenarian liver grafts presented significantly lower five-year graft survival compared to HCV-negative octogenarian liver recipients (62.4% vs. 85.6%, respectively; P 0.03) according to the findings of Ghinolfi et al. [38] In addition, an HCV-positive status was an independent risk factor of graft loss in multivariate analyses (HR 1.749; 95% CI 1.28–2.38; P 0.001). Cescon et al. [39] published similar results (OR 2.08; 95% CI 1.49–2.90; P 0.001). Zapletal et al. [40] reported a 100% re-infection rate following liver transplantation in HCV-positive recipients who received octogenarian livers. HCV-positive patients who received older grafts (≥ 80 years) had non-significantly lower graft survival but presented with a significantly lower survival rate compared to HCV-positive patients who received younger grafts (≤ 40 years) (40% vs. 81.7%; P 0.05, respectively) as published by Nardo et al. [31]; in this study, the most frequent cause of death among the older liver recipients was HCV recurrence.

4. Discussion

This is the first systematic review and meta-analysis comparing the outcome of LTx from donors aged ≥80 years old with those from younger donors displayed similar results and complication rates, except for BCs. There were no differences in the one, three and five-year patient and graft survival. Moreover, the PNF, VC and re-LTx rates were comparable. The only difference appeared to be in the frequency of BCs between groups in favour of younger livers (< 80 years). This finding is interesting as a meta-analysis published by the Dasari et al. did not confirm an increased risk of BCs for septuagenarian liver transplants [22] On the other hand, advanced donor age has been reported as a risk factor of BCs in both deceased and living donor LTx [41]. Serrano et al. [7] demonstrated that a donor age ≥ 60 years is an independent risk factor for intrahepatic non-ischemic strictures (OR 15.4; 95% CI 1.42–168.1; P 0.02). In addition, the older donor group had four times more frequent ITBL in comparison to the younger donor group. According to Ghinolfi et al. [42], older liver grafts are more sensitive to hemodynamic instability during procurement, which may increase the injury of biliary tree and therefore results in the higher rate of BCs. However, appropriate donor selection and donor-to-recipient matching can reduce complications and improve outcomes. Moreover, the authors suggest that livers from older donors with hemodynamic instability and a history of diabetes mellitus are more prone to developing ITBL. These factors combined with a high MELD score recipient leads to worse graft survival. Thus, older livers should not be allocated to high-MELD recipients. Interestingly, recipients of octogenarian livers presented lower MELD scores in most studies included in the current meta-analysis [32,33,37,38]. This suggests that the pathogenesis of BCs is highly complex and many factors contribute to the development of BCs [43].

Feng et al. proposed that the donor age is an important component of DRI [36] and suggested that donor age is a strong risk factor for graft failure. According to the current analysis, there were no more PNF episodes in the older liver transplants, and graft survival did not differ between the recipient groups. In contrast, the analysis published by Halazun et al. proved that every 10-year increase in donor age causes significant decrease in graft survival after LTx [44].

There are several factors that may impact the long-term graft survival and function. Typically, these are described as donor-dependent factors, perioperative factors and recipient-dependent factors, and some them can be modified, however most of them cannot. With regards to donor factors, there is surprisingly not one test or examination that will determine whether the organ will be used, however machine perfusion is increasingly used for the graft assessment [45]. The combination of donor-derived parameters (including age) and the macroscopic evaluation of organs by a donor surgeon with the balance of recipient-derived parameters are used in conjunction to decide the final organ procurement. This review and meta-analysis confirms that advance age alone should not determine the decision regarding liver acceptance or denial.

The interesting approach for impact of donor age on results of LTx has been published recently by Bittermann et al. [46] The impact of donor age on results of LTx was more pronounced in younger recipients and the authors suggested changing the allocation policy in order to match high-quality organs to younger recipients.

As mentioned previously, the advanced donor age and HCV-positive status of the recipient is detrimental for the outcome. In most cases, HCV-positive patients who receive older liver grafts were associated with worse graft survival [31,38,39] and occasionally presented with more complications [28]. In the analysis by Lake et al. [47], donor age was the strongest predictor of graft loss. Interestingly, according to results published by Gajate et al. [33], the most recent study included in this review, no significant differences were found regarding graft survival for octogenarian liver HCV-positive recipients. The introduction of new direct-acting antiviral agents (DAA) against HCV has changed the negative outcome for HCV-positive patients. There are fewer HCV-positive patients referred to the liver transplant waiting list, the survival rate has improved and the reinfection rates following LTx are decreasing [48]. In previous analyses, older liver grafts were not recommended for HCV-positive recipients [19]; however, the use of DAA against HCV is changing this policy. Finally, it is important to note that there is an urgent need to develop the allocation policy of octogenarian liver grafts and new recommendations should be applied in clinical practice.

The current review and meta-analysis has several limitations. In particular, there are no randomized controlled trials available, as they would be extremely difficult to conduct, if possible at all. Thus, all of the included studies are retrospective comparative analyses of moderate quality. The study is limited only to eight studies that were published and applicable for the analysis. Moreover, there are substantial differences between the studies regarding the number of cases, follow-up periods and periods of data collection. The heterogeneity between the studies included in the meta-analysis was observed. Significant heterogeneity (≥ 65%) was present for three-years and five-years graft survival as well as for re-transplantation analysis.

Despite of aforementioned limitations this review and meta-analysis summarizes the current knowledge and practise with LTx from octogenarian donors allows drawing some prudent conclusions. Finally, there is a strong necessity to develop recommendations and guidelines for the octogenarian graft allocation policy in order to determine which recipient benefits the most and under which conditions.

5. Conclusions

The short- and medium-term graft and patient survival of octogenarian liver transplantation is not inferior compared to the liver transplantation with younger grafts when proper donor selection and good recipient match is used. The lack of differences in PNF, VC and re-LTx confirms that octogenarian donors are valuable source of organs, however these liver grafts prone to developing more BCs compared with younger grafts.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.trre.2019.06.004.

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