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Risk factors for developing Post-Transplant Lymphoproliferative Disorder in children after renal transplantation

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Introduction

Post-transplant lymphoproliferative disorder (PTLD): lymphoma after Tx

- Worldwide PTLD incidence 1-3%[1]
  - → PTLD incidence in children after renal transplantation: 1.2%-10.1%[1]

Related to EBV infection

- Double-stranded DNA human Herpes Virus
- Seroprevalence adults worldwide: 90-95% [2]
- In pediatrics: mostly primary infection after Tx
  - Seropositive donor → seronegative recipient
- Seronegativity at time of Tx identified as risk factor for PTLD[3]

[1]Taylor AL, Marcus R, Bradley JA. Post-transplant lymphoproliferative disorders (PTLD) after solid organ transplantation
[2]M.Green et al., Epstein-Barr Virus Infection and Posttransplant Lymphoproliferative Disorder
[3]Cockfield SM. Identifying the patient at risk for post-transplant lymphoprolif- erative disorder. Transpl Infect Dis 2001; 3:70-8

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Aim of the study

Many different potential risk factors, like age and immunosuppression have been identified. However studies show divergent outcomes.

With the high PTLD incidence in pediatrics, it is necessary to verify these potential risk factors.

Therefore the goal of this review is to determine the risk factors for PTLD development after pediatric renal transplantation.

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Materials & Methods

Search strategy: Pubmed to October 2017

- EBV
  - Herpesvirus 4, Human, Epstein-Barr Virus Infections, EBV
- Renal Transplantation
  - Kidney Transplantation
- Pediatrics
  - Pediatrics, Child
- PTLD
  - PTLD, Lymphoproliferative Disorders

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Materials & Methods

Inclusion criteria:

- Articles must describe one or more of the following risk factors: EBV load, seroconversion, immunosuppression and age
- Age barrier set at 18 years
- Kidney transplants only

Exclusion criteria:

- Articles which had included other solid organ transplantations in the results
- Case reports
- Articles which combined or compared the results of children and adults

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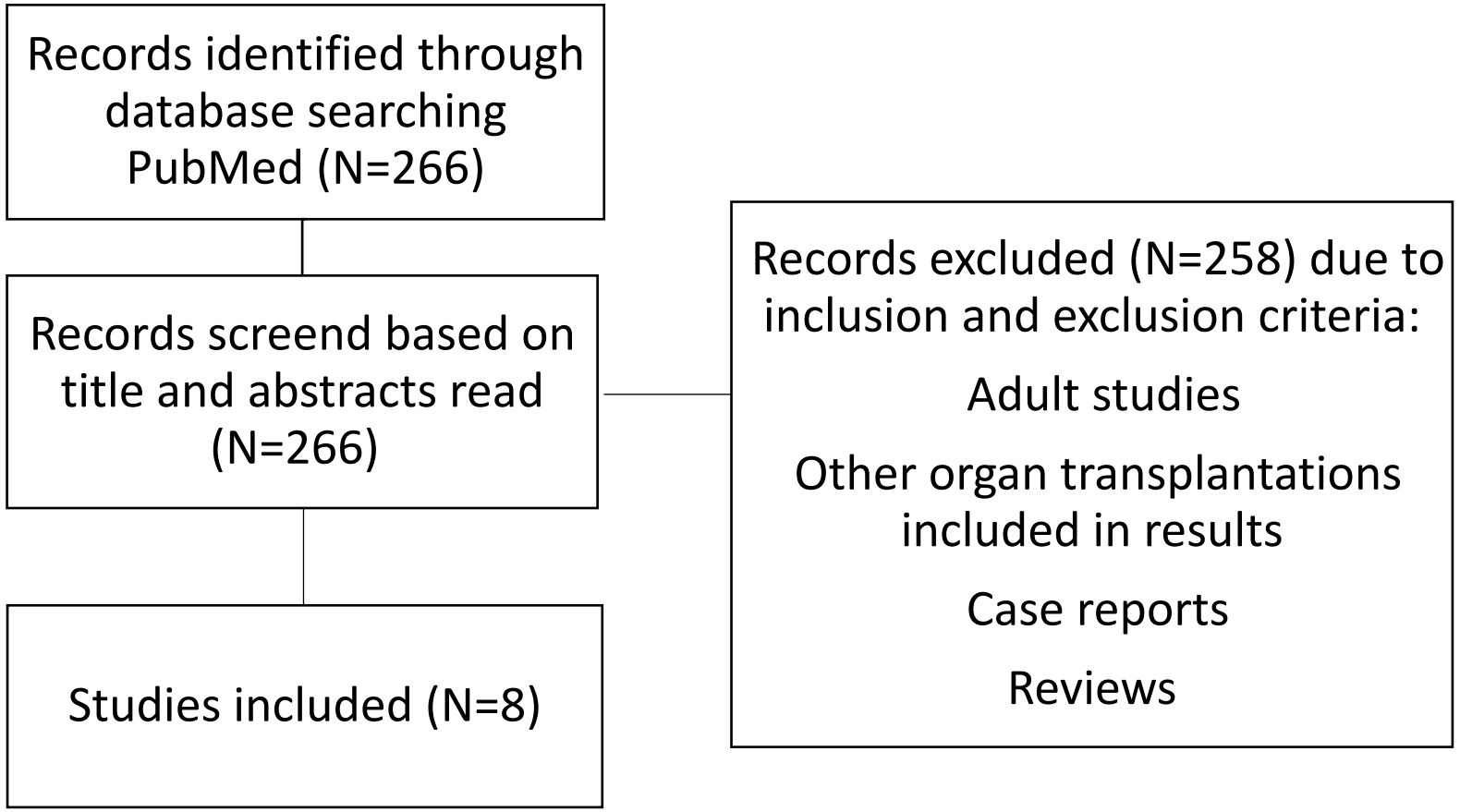
Results



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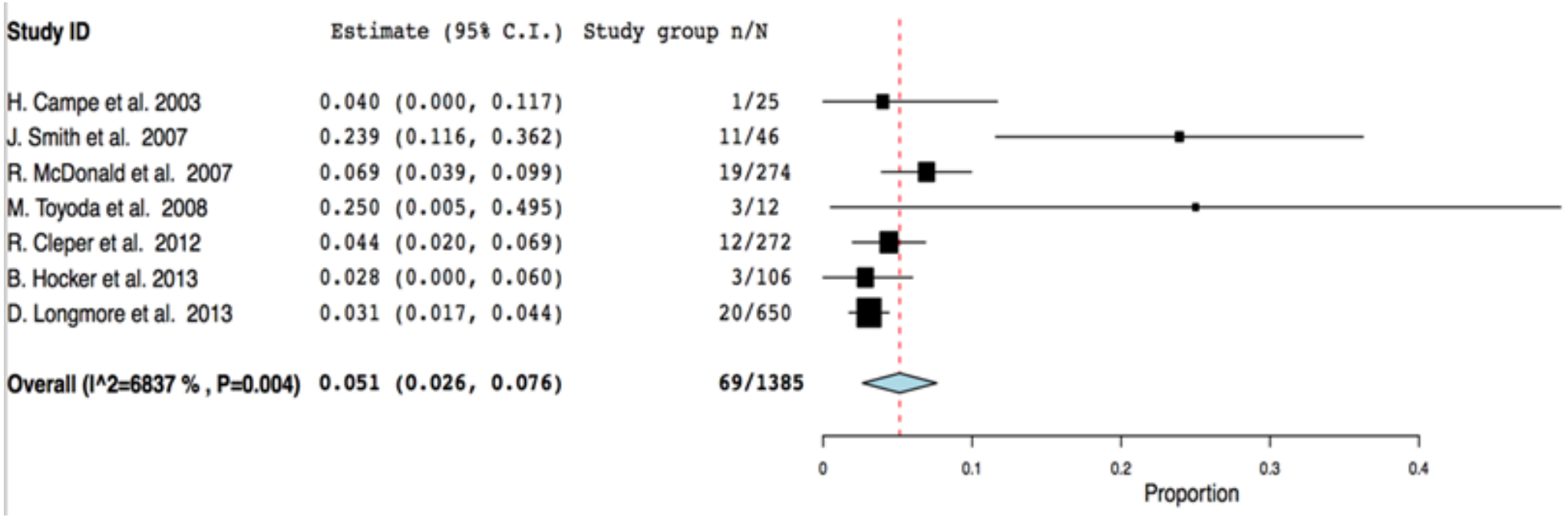
Included studies

	Year of publication	Country	Population (N)	Age at Tx (Yrs)	Incidence PTLD	Evaluated as potential risk factors
H. Campe et al.	2003	Germany	25	Not shown	4% (N=1)	EBV load
G. Opelz et al.	2003	Germany	Not shown	Not shown	Not shown	Immunosuppression
J. Smith et al.	2007	USA	46	12.4	24% (N=11)	EBV load, Seroconversion, Age
R. McDonald et al.	2007	USA	274	Not shown	7% (N=19)	Seroconversion, Immunosuppression, Age
M. Toyoda et al.	2008	USA	58	Not shown	25% (N=14)	EBV load, Seroconversion
R. Cleper et al.	2012	Israël	272	4.2	4% (N=12)	Seroconversion, Immunosuppression
D. Longmore et al.	2013	Australia	650	8	3% (N=20)	Age
B. Höcker et al	2013	Germany	106	5.9	3% (N=3)	EBV load, Seroconversion, Immunosuppression
TOTAL			>1.385		>69	

Incidence of PTLD



Calculated mean incidence from included studies: 5.1%

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Results

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EBV load

	Mean PCR load with PTLD	Mean PCR load without PTLD	Viral loads in PTLD cases (*p-value*)
B. Höcker et al.	Not mentioned	Not mentioned	*Lower, p = 0.60, p=0.91*
M. Toyoda et al.	131 copies/PCR	87 copies/PCR	*p = n.s.*
J. Smith et al.	10400 copies/mL	Symptomatic EBV: 2750 copies/mL Asymptomatic EBV: 560 copies/mL	*Higher, p = 0.02*
H. Campe et al.	Not shown with PTLD	Symptomatic EBV: 22500 copies/mL Asymptomatic EBV: 13250 copies/mL	*p = n.s.*

Seroconversion

- Serostatus: seronegativity associated with higher PTLD incidence (*J. Smith et al., R. McDonald et al.*)

	Seroconversion in EBV-naïve patients	Seroconversion in EBV-naïve patients after initial EBV viremia	Time till developing PTLD post-Tx
B. Höcker et al.	7.5 ± 2.3 months	4.9 ± 3.3 months	6 months
M. Toyoda et al.	17.7 ± 3.3 months	Not mentioned	Not mentioned
J. Smith et al.	Not mentioned	Not mentioned	11 months
R. Cleper et al.	Not mentioned	Not mentioned	39 months
R. McDonald et al.	Not mentioned	Not mentioned	7.2 months

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Results

Young Age

	Outcome
McDonald et al. *(N=274)*	0-5 yrs group is at higher risk (*p = 0.0017*)
Smith et al. *(N=46)*	12-18yrs group are at higher risk *(p = 0.05*)
D. Longmore et al. *(N=650)*	No higher risk for any age group (*p = n.s.)*

Immunosuppression

	AZA	CsA	TAC	OKT3
B. Höcker et al. (N=106)		-	-	
R. Cleper et al. (N=272)	-		-	+
R. McDonald et al. (N=274)		-	-	
G. Opelz et al. (N=?)	-	-		+

- *B. Höcker et al.:* MMF therapy → lower risk of EBV viremia (*HR=0.52; 95% CI, .31– 0.88; P= 0.014*)

Conclusion

The PTLD incidence is 5.1%

No data that supports EBV load is a risk factor

Data that supports immunosuppression is a risk factor is not conclusive

There's no data that clearly suggests that children of a certain age are at increased risk for PTLD development

Necessary now:

- Large scale studies including registry studies which accurately register viral load, induction therapy and immunosuppression.

  → Which children should not be transplanted due to risk factors and which immunosuppressants should not be used.

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Acknowledgements

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