THE FORUM
For Collaborative Research℠

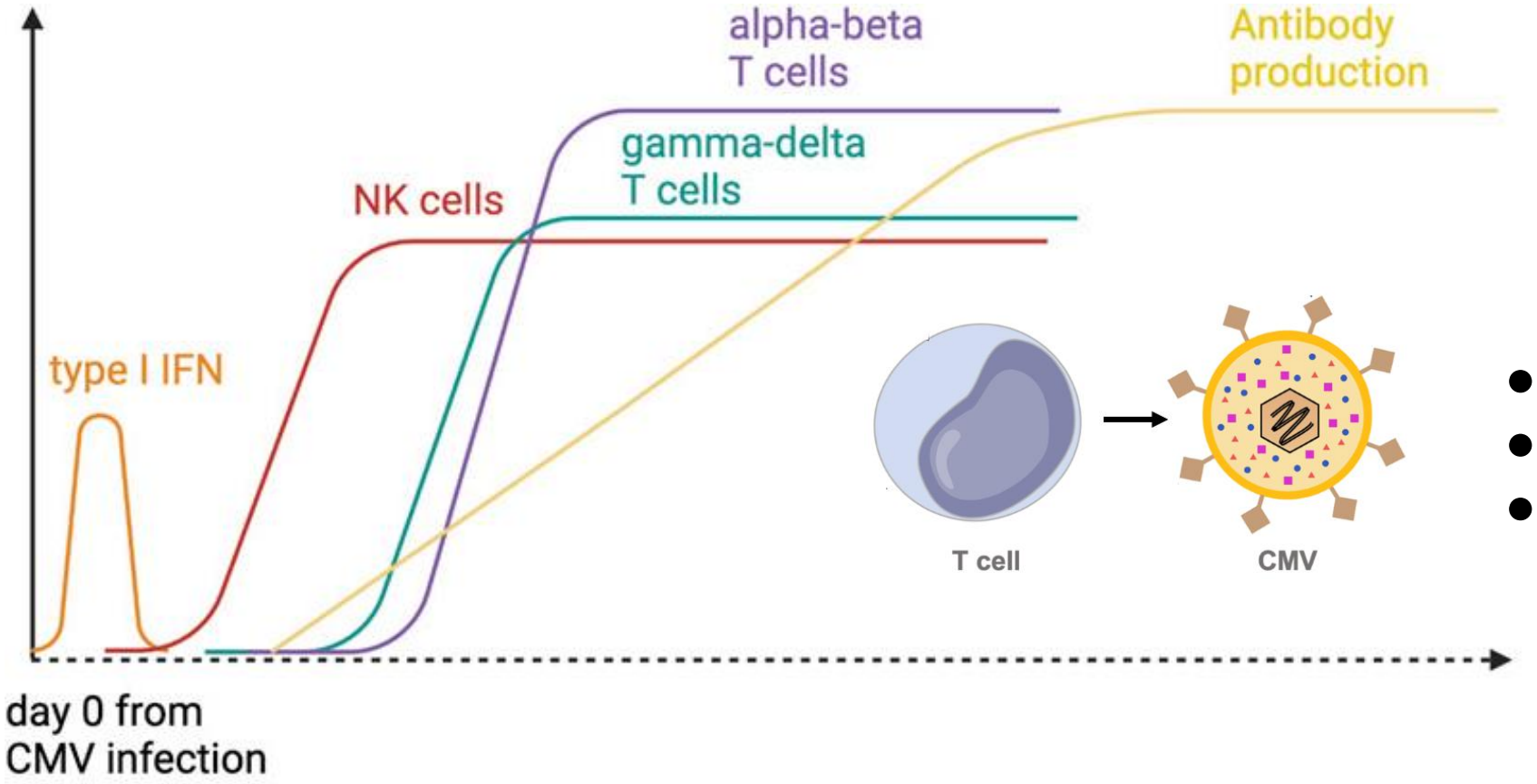
Predicting Cytomegalovirus Outcomes in Transplantation: Is Cell-Immune Monitoring Ready for Clinical Use? A systematic review.

Frédérique Sauvé*, Cesar G. Berto*, Yoichiro Natori, Aasith Villavicencio Paz, Angela Monahan, Shilpa Mitra, Veronica Miller, John Reynolds, Per Ljungman, Roy Chemaly, Camille N. Kotton

Cesar G. Berto, MD
Massachusetts General Hospital

Berkeley Public Health

Introduction

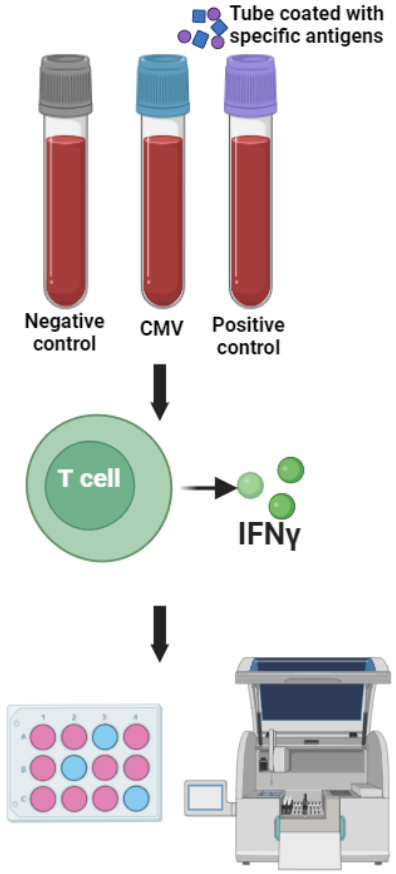


- When?
- In whom?
- Which method?

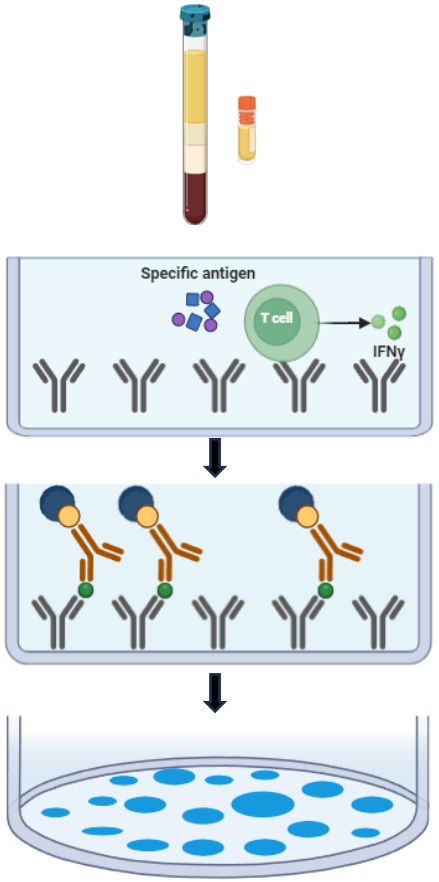
- Bestard O, Kaminski H, Couzi L, Fernández-Ruiz M, Manuel O. Cytomegalovirus Cell-Mediated Immunity: Ready for Routine Use? Transpl Int. 2023;36:11963.
- Stewart AG, Kotton CN. What's New: Updates on Cytomegalovirus in Solid Organ Transplantation. Transplantation. 2024;108(4):884-97.

Introduction

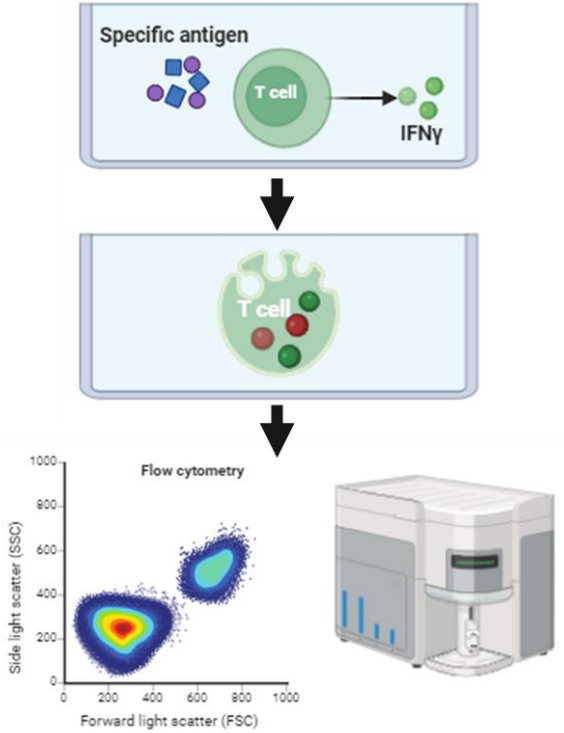
QuantiFERON



EliSPOT



Flow cytometry ICS



- Created with BioRender.com, adapted from “ELISpot Assay Protocol”, by BioRender.com (2024). Retrieved from https://app.biorender.com/biorender-templates

Methods

Inclusion

Population
- SOT - all types
- D+/R- & R+

Index test
- EliSPOT
- QuantiFERON
- Intracellular cytokine staining

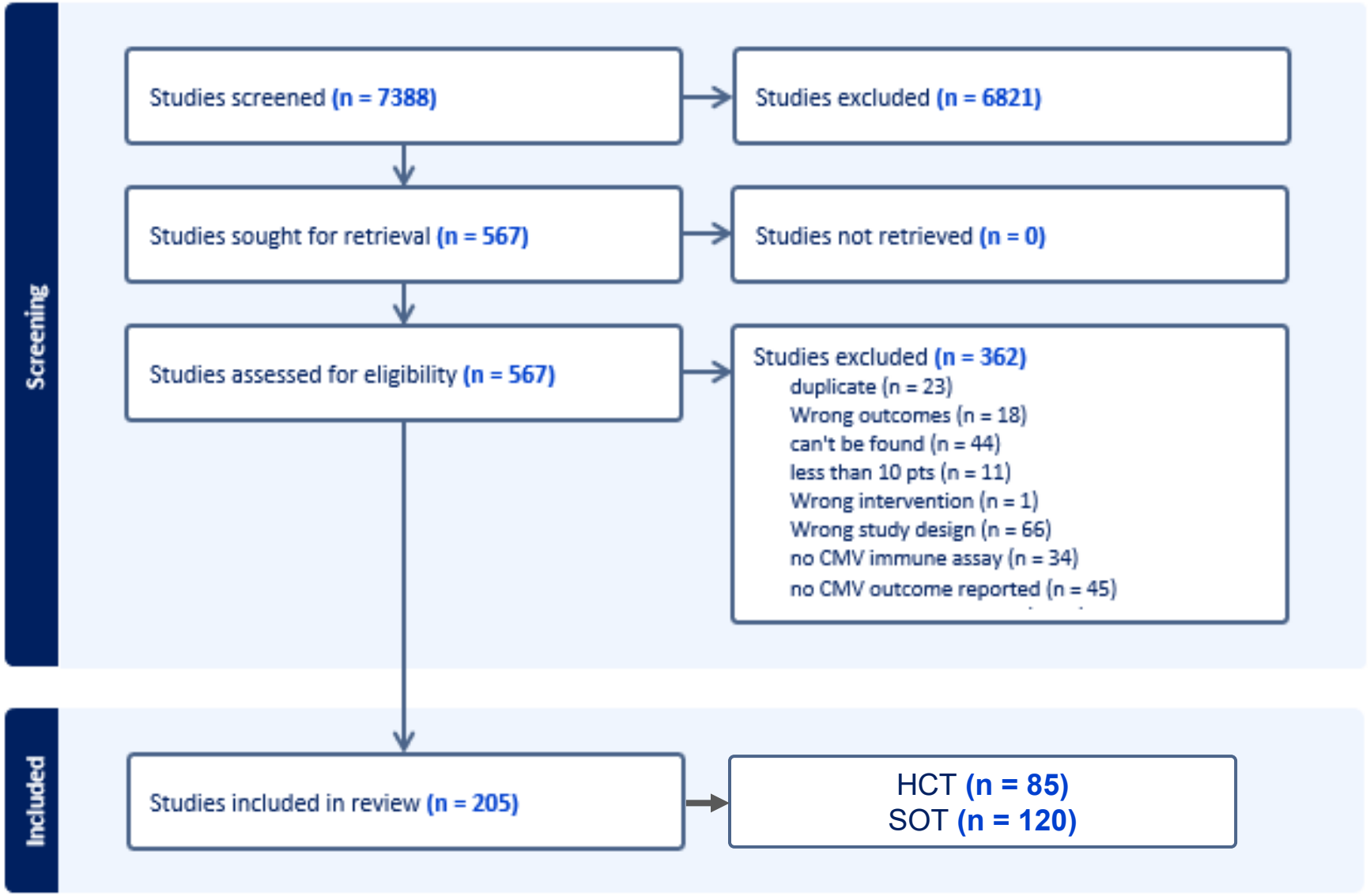
Target condition
- CMV infection (antigenemia or DNAemia)
- CMV disease

Exclusion

Population
- HSCT or other IS condition
- < 10 participants

Index test
- Cytokine profile studies without quantification
- Lack of uniform timing

Target condition
- No CMV related outcome reported


Screening
Studies screened (n = 7388)
Studies excluded (n = 6821)
Studies sought for retrieval (n = 567)
Studies not retrieved (n = 0)
Studies assessed for eligibility (n = 567)
Studies excluded (n = 362)
duplicate (n = 23)
Wrong outcomes (n = 18)
can't be found (n = 44)
less than 10 pts (n = 11)
Wrong intervention (n = 1)
Wrong study design (n = 66)
no CMV immune assay (n = 34)
no CMV outcome reported (n = 45)
Included
Studies included in review (n = 205)
HCT (n = 85)
SOT (n = 120)

Layout

Clinical question	Outcome
Pre-transplant	
-Can Cell-mediated immunity (CMI) before transplant predict the risk of CMV-related outcomes?	CMV infection/disease
Related to universal prophylaxis	
-Can CMI at the end of prophylaxis predict the risk of CMV-related outcomes? -Can CMI during prophylaxis inform the optimal duration of prophylaxis?	Late-onset CMV infection/disease
Related to pre-emptive treatment	
-Can CMI differentiate those who will have spontaneous clearance of viremia from those who require to start therapy?	Spontaneous clearance
After first episode of CMV infection	
-Can CMV-CMI at the end of treatment for CMV infection predict the risk of CMV relapse?	Post-treatment CMV relapse

First Author, year	Sample size	Transplant type	Serostatus	Immune assay	Results
Ashokkumar, 2019	142	multiple	unknown	ICS	positive
Carbone, 2012	38	heart	R+	ICS	positive, significant
Litjens, 2017	42	kidney	D+/R- and R+	ICS	positive, significant
Fernandez-Ruiz, 2019	124	kidney	R+	ICS	positive, significant
Abate, 2012	58	heart	R+	ELISPOT	positive, significant
Youn, 2017	35	heart	unknown	ELISPOT	positive, significant
Garcia-Romero, 2019	29	heart	R+	ELISPOT	positive
Costa, 2015	80	kidney	unknown	ELISPOT	positive
Jarque, 2020	160	kidney	R+	T-SPOT	positive, significant
Fornara, 2016	29	kidney	unknown	ELISPOT	positive, significant
Kim, 2020	133	kidney	D+/R-, R+, D-/R-	ELISPOT	positive, significant
Lucia , 2014	129	kidney	D+/R-, R+, D-/R-	ELISPOT	positive, significant
Schachtner, 2017	326	kidney	D+/R-, R+, D-/R-	ELISPOT	mixed
Jarque, 2017	317	kidney	D+/R-, R+, D-/R-	ELISPOT	positive, significant
Shin, 2018	32	liver	R+	ELISPOT	no association
Lee, 2017	124	kidney	R+	multiple	mixed
Kwon, 2017	47	kidney	R+	QuantiFERON	no association
Pongsakornkullachart, 2022	55	kidney	R+	quantiFERON	no association
Fernandez-Ruiz, 2020	120	kidney	R+	QuantiFERON	no association
Bhugra, 2023	30	liver	R+	QuantiFERON	positive, significant
Cantisan, 2013	55	multiple	D+/R-, R+, D-/R-	QuantiFERON	positive, significant
Zielinski, 2016	52	kidney	D+/R-, R+, D-/R-	ICS	positive, significant
Mena-Romo, 2017	106	multiple	R+	ICS	positive, significant
Molina-Ortega, 2019	135	multiple	R+	ICS	positive, significant
Lopez-Olivia, 2020	28	kidney	R+	ICS	mixed
Banas, 2017	86	kidney	R+	T-Track CMV	no association
Reischig, 2013	95	kidney	D+/R- and R+	ELISpot	positive

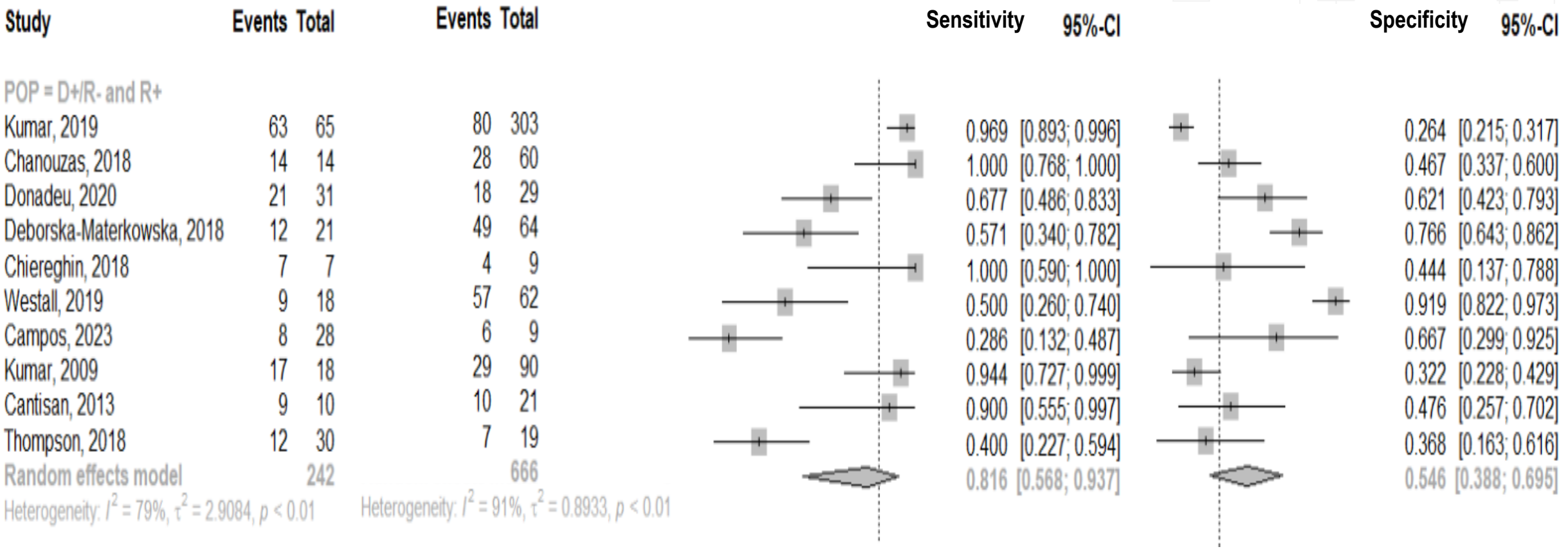
- 5 out of 27 studies found no association between assay result and risk of CMV infection
- ELISPOT and ICS showed the best results, while QuantiFERON showed no association in 60% of the studies.
- Predictive value of the assay did not seem to correlate with serostatus, although hard to assess considering only 2 studies included D+/R- patients only

Sensitivity and Specificity

- Sensitivity
  - Proportion of patients who developed CMV infection after negative CMV-CMI / all with CMV infection

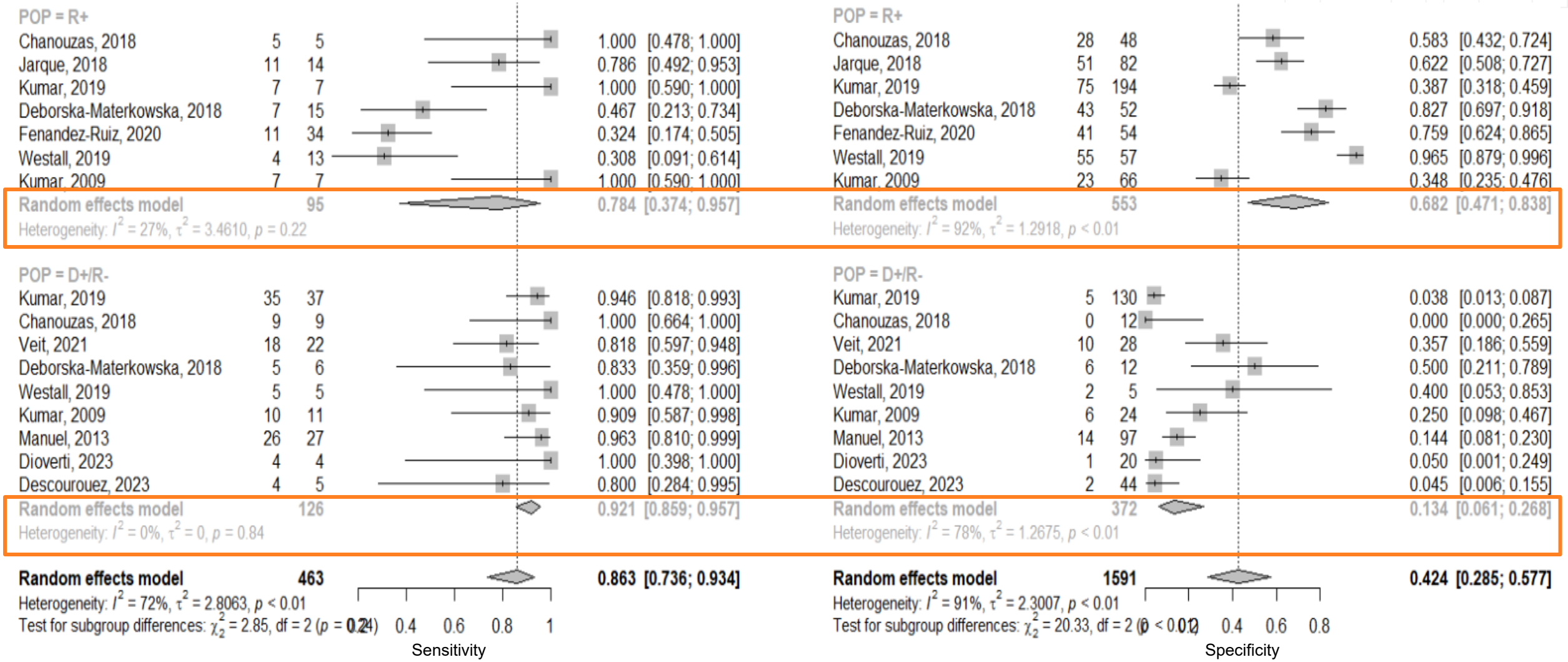
- Specificity
  - Proportion of patients who remained infection-free after a positive CMV-CMI / all who are infection-free

End of prophylaxis (Total population)



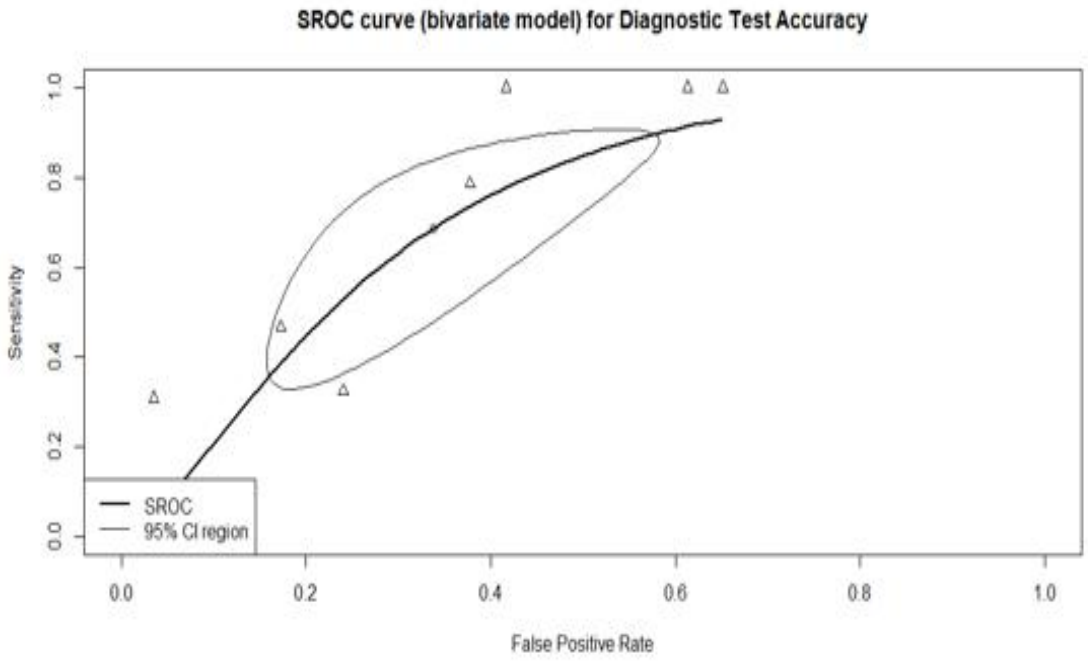
- Sensitivity 81.6% & Specificity 54.6%
- High heterogeneity between studies

End of prophylaxis by subgroup



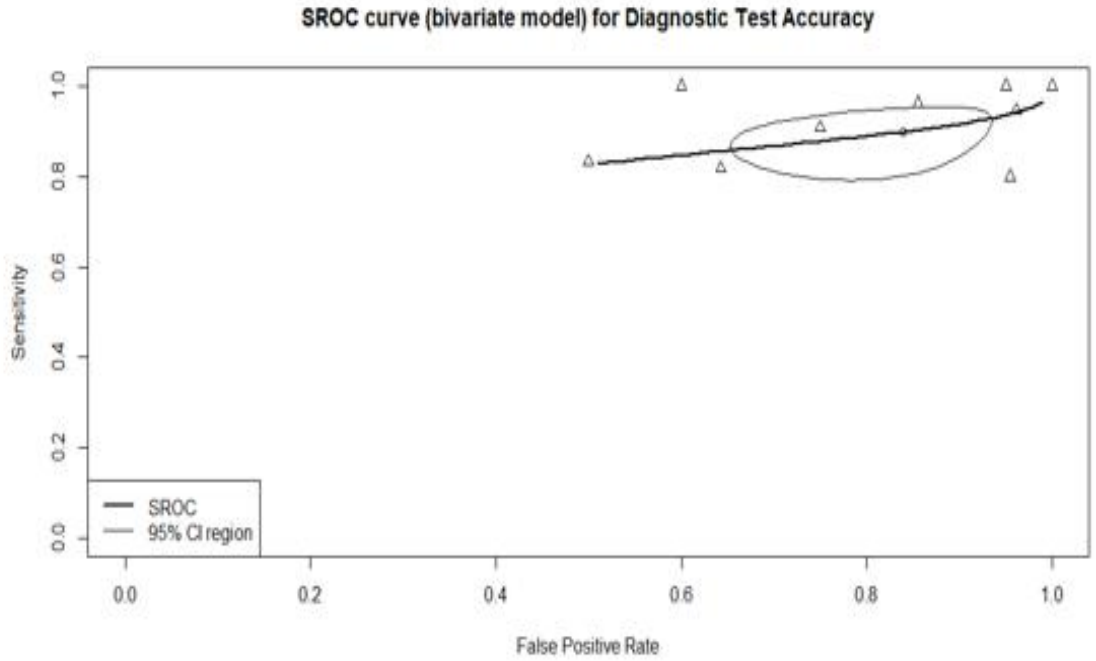
End of prophylaxis by subgroup

R+



- High heterogeneity
- AUC 0.64

D+/R-



- ↑ AUC but limited specificity
- ↓ rate of positivity in this group

QUADAS-2 – Assessment of quality of studies

Study	Risk of bias				Applicabilty concerns		
	Patient selection	Index test	Reference Standard	Flow and Timing	Patient selection	Index test	Reference standard
Kumar, 2019	☺	☹	☺	☺	☺	☹	☺
Chanouzas, 2018	☺	☹	☺	☺	☺	☹	☺
Donadeu, 2020	☺	☹	☺	☺	?	☹	☺
Deborska-Materkowska, 2018	☺	☺	☺	☺	☺	☺	?
Chiereghin, 2018	☺	☺	☺	☺	?	☺	☺
Westall, 2019	☺	☺	☺	☺	☺	☺	☺
Campos, 2023	☺	☺	☺	☺	?	☺	?
Kumar, 2009	☺	☺	☺	☺	☺	☺	?
Cantisan, 2013	☺	☺	☺	☺	?	☺	?
Thompson, 2018	☺	☺	☺	☺	?	☺	?

Optimal duration of prophylaxis

Author, year	Country	N	Organ	CMV serology	Induction ATG (%)	CMI	Timing	Results
Paez-Vega, 2022	Spain	150	Kidney	R+	ATG (100%)	QuantiFERON-CMV	3 months vs CMI-guided (1-3 months)	No difference in rate of CMV infection
Manuel, 2024	Switzerland	185	Kidney Liver	R+ and D+/R-	ATG (55.7%)	T-TRACK® CMV	3 mo. for R+ or 6 mo. for D+/R- vs CMI-guided (1-6 months)	Slightly higher rate of CMV infection in CMI-guided
Westall, 2019	Australia	118	Lung	R+ and D+/R-		QuantiFERON-CMV	5 months vs CMI-guided (5-11 months)	No difference in CMV infection Lower rate of CMV lung allograft in CMI-guided
Gardiner, 2022	Australia	263	Lung	R+ and D+/R-		QuantiFERON-CMV	5 months vs CMI-guided (5-11 months)	No difference in CMV infection Lower rate of CMV lung allograft in CMI-guided
Poglajen, 2020	Slovenia	154	Heart	R+ and D+/R-		QuantiFERON-CMV	3 months vs CMI-guided (3-9 months)	Lower rate of CMV infection in CMI-guided
Solera, 2022	Canada	108	Multiple	R+ and D+/R-	ATG	QuantiFERON-CMV	3 months vs CMI-guided (3-6 months)	D+/R-: Only 1/39 with + CMI R+: No difference in CMV infection

- Could be considered to shorten prophylaxis duration in R+.
- Additional studies are required for LTx (comparison to standard prophylaxis).
- Low frequency of positive results in D+/R-.

Post-treatment relapse

First author, year	Country	Sample size	Organ	CMV serology	Induction	CMI	Results
Dioverti, 2023	United States	24	Multiple	D+/R-	ATG (33.3%)	QuantiFERON-CMV	Positive, significant
Sermet, 2023	France	15	Heart	Mix	ATG (93%)	QuantiFERON-CMV	No difference
Chiereghin, 2018	Italy	44	Heart	R+	ATG (85%)	QuantiFERON-CMV	Positive, significant
Rogers, 2020	United States	31	Multiple	Mix		Viracor CMV-T-cell immunity panel	Positive, not significant
Descourouez, 2023	United States	27	Kidney Pancreas	D+/R-	ATG (69.7%)	Viracor CMV-T-cell immunity panel	No difference
Pipeling, 2011	United States	22	Lung	D+/R-		ICS	Positive, not significant
Jorgenson, 2020	United States	25	Multiple	Mix		ICS	Positive, significant
Kumar, 2017	Canada	27	Multiple	Mix	ATG (22.2%)	QuantiFERON-CMV	Positive, significant

- QF could be helpful to identify those at higher risk of relapse but more studies are required.
- Conclusion from ICS are less clear.
- Additional clinical trials are required in this subgroup.

Conclusion

- There is significant **heterogeneity** between studies; different CMI, cut-off, population and timing.
- Current data is **limited** to make a generalized conclusion on their use.
- **In selected groups**, CMI at the time of transplant, at the end of prophylaxis and at end of therapy could help to stratify risk.

Acknowledgments

- Mentorship/guidance
  - Drs. Veronica Miller, Yochiro Natori, Camille Kotton, Roy Chemaly
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