



THE FORUM
For Collaborative ResearchSM

Ability of cytomegalovirus immune monitoring assays to predict CMV related outcomes in transplant patients: a systematic review

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Forum for Collaborative Research

Berkeley Public Health

■ Inclusion

Patient population

- HSCT - both allo and auto
- SOT - all types
- >10 patients or at least 10 patients that meet the study criteria

Tests

- ELISPOT and derivatives (T-SPOT, Elisa)
- Quantiferon and derivatives
- intracellular cytokine staining with flow cytometry
- Other tests such as “homemade” tests.

Patient outcomes included:

- Change in treatment management
- CMV infection
- viral load positivity (just viremia is ok)
- Antigenemia
- Reactivation
- Clinical symptoms of CMV

Study type

- Observational studies
- Interventional studies
- Stored specimen studies
- Poster/conference abstract with sufficient data

■ Exclusion

Patient population

- not HSCT and/or
- not SOT
- <10 patients

Tests

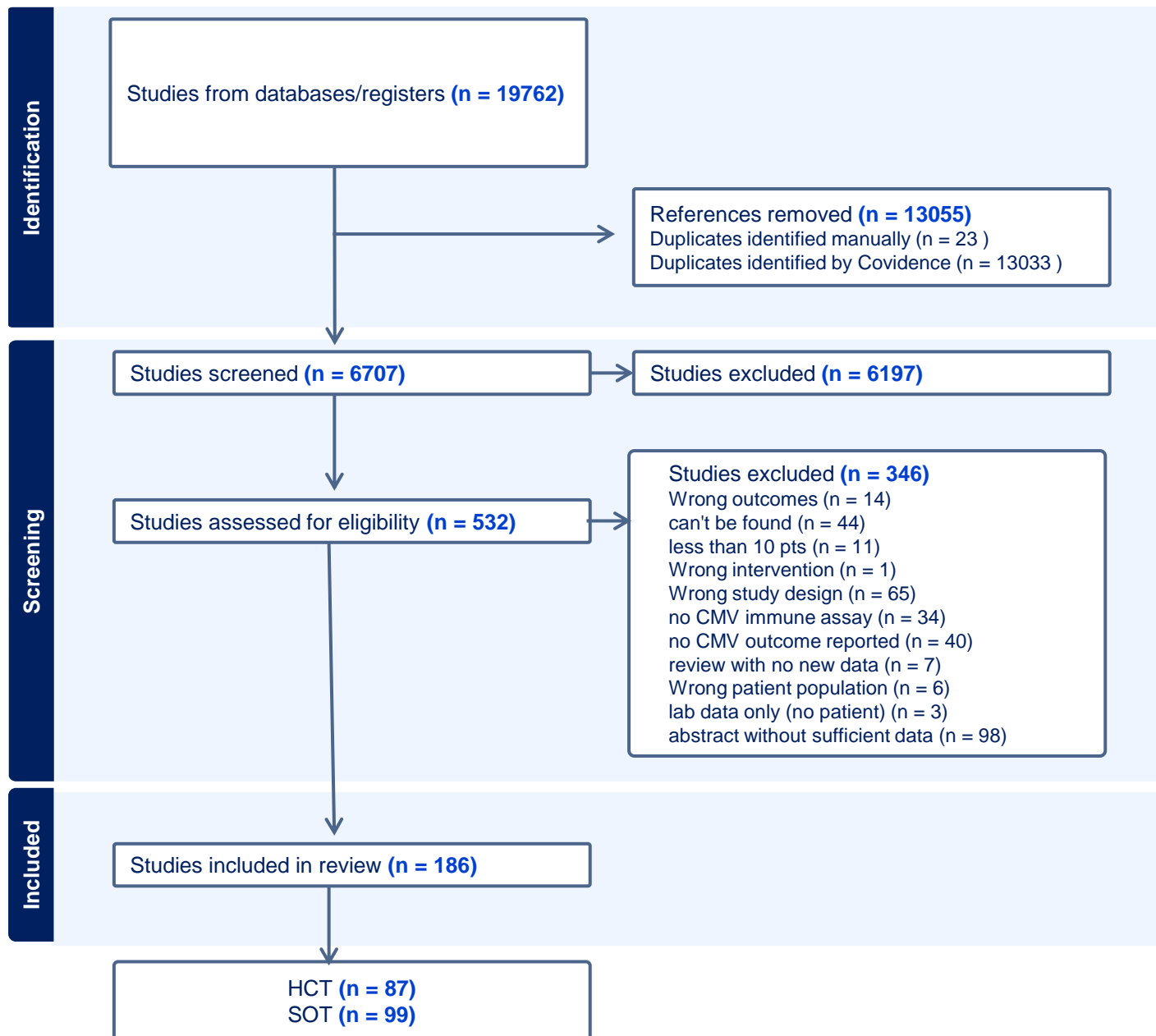
- No quantitative CMV immune assay reported
- Cytokine profiles studies without quantification

Patient Outcomes

- No CMV related outcome reported

Types of studies:

- Poster/conference abstract with insufficient data
- Review without new data
- Laboratory based studies without patient information
- Natural history studies
- Animal Studies
- duplicates

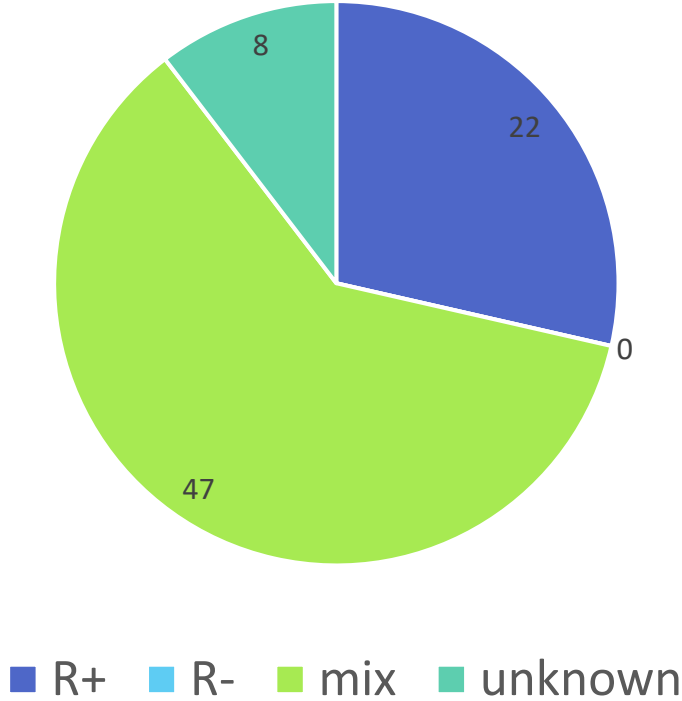


Extraction = 186 papers, 99 SOT: 87 HCT

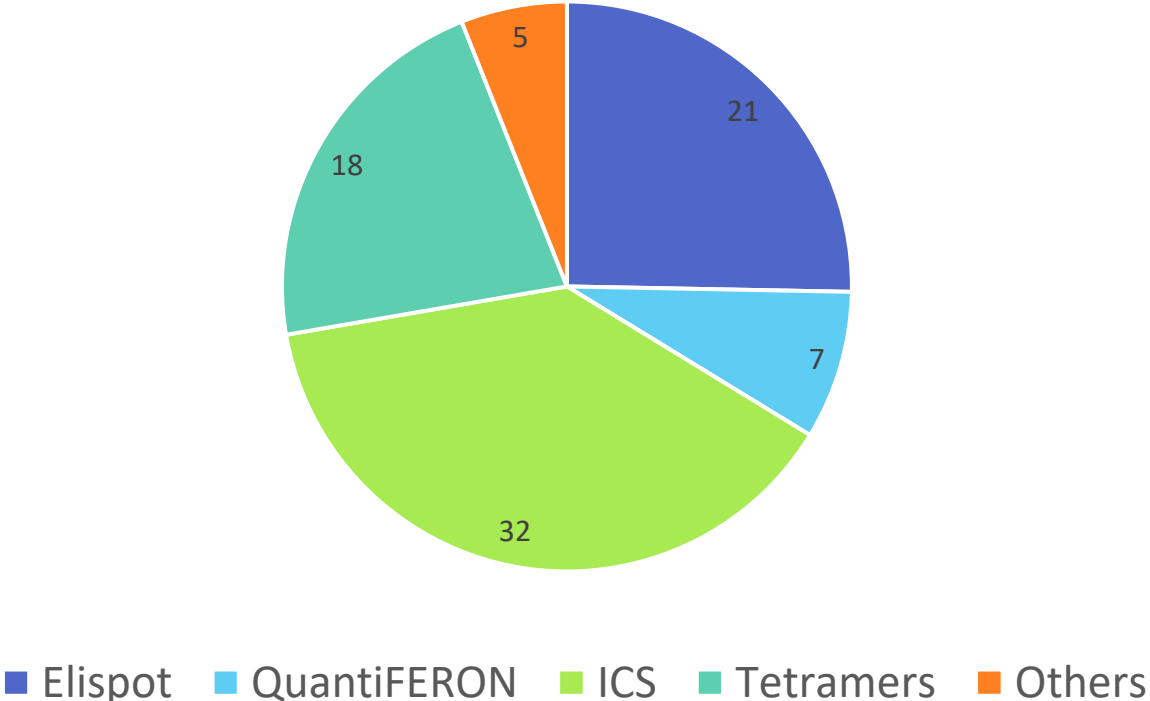
Article DOI	Author	year	title	sample size	type of transplant	patient gender	patient age	Serostatus	patient outcome recorded
https://doi.org/10.1128/JCM.06406-11	Davide Abate, Marta Fiscon, Alda Saldan, Simona Cofano, Carlo Mengoli, Dino Sgarabotto, Chiara d'Agostino, Luisa Barzon, Riccardo Cusinato, Giuseppe Toscano, Giuseppe Feltrin, Antonio Gambino, Gino Gerosa, Giorgio Palù	2012	Human Cytomegalovirus-Specific T-Cell Immune Reconstitution in Preemptively Treated Heart Transplant Recipients Identifies Subjects at Critical Risk for Infection	58	48 heart transplants, 10 pre-transplant	female: 8, male: 40	median: 59 (11-74)	R+D+ and R+D-	CMV infection is defined as detection of viremia at >1,000 copies/ml of whole blood. CMV disease was defined as symptomatic clinical manifestations with fever and malaise associated with detectable CMV viremia and not ascribable to any other infection or condition
type of assay	assay threshold studied	PPV, NPV, sensitivity, specificity	antigen studied	timing	assay results vs patient outcome	conditioning regimen	antiviral treatment		
ELISPOT	50 and 100 spots	NA	pp65	Twenty-nine patients were analyzed both before and after 100 days posttransplant, while 19 patients were analyzed once for collection of a single data point before or after 100 days posttransplant	Patients protected from CMV viremia displayed statistically significantly higher ELISPOT levels (median, 173 spots; range, 0 to 1,000 spots) than HTXs with the occurrence of viremia (median, 18 spots; range, 1 to 267 spots). On the basis of the ELISPOT levels, we arbitrarily grouped HTXs into high responders (>100 spots), midresponders (>50 to <100 spots), and low responders (<50 spots) (p<0.05)	antithymocyte treatment (recombinant antithymocyte globulin, 20 mg/kg of body weight/day) for 4 days posttransplant	transplant patients were treated according to a preemptive strategy, defined as described previously (21, 29, 35, 37) and consisting of the initiation of antiviral treatment upon the detection of a viral load (CMV DNAemia) above 5,000 copies/ml. Anti-CMV preemptive treatment included oral administration of valganciclovir (Valcyte; Roche) at a standard dose (900 mg twice a day) or intravenous ganciclovir (5 mg twice a day) corrected according to renal function.		

Summary HCT

Serostatus

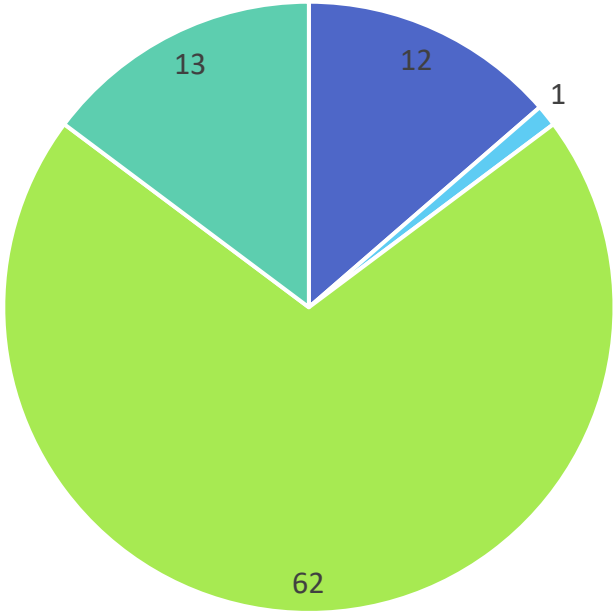


Type of Assays



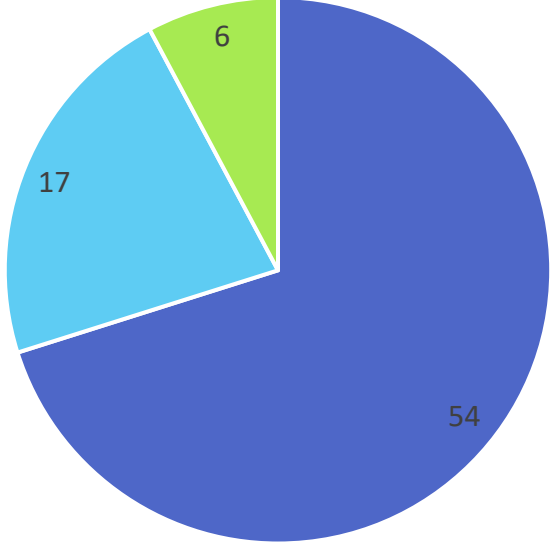
Summary HCT

Timing



- at transplant
- end of prophylaxis
- serial time points
- one time point

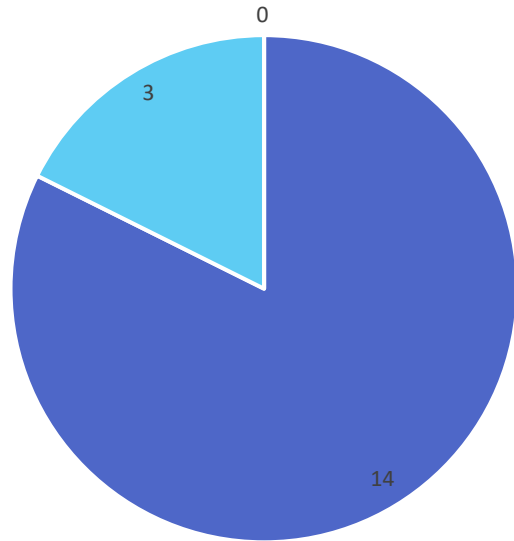
Association



- Positive Significant Prediction
- Positive Non-Significant Prediction
- Negative/ Null Prediction

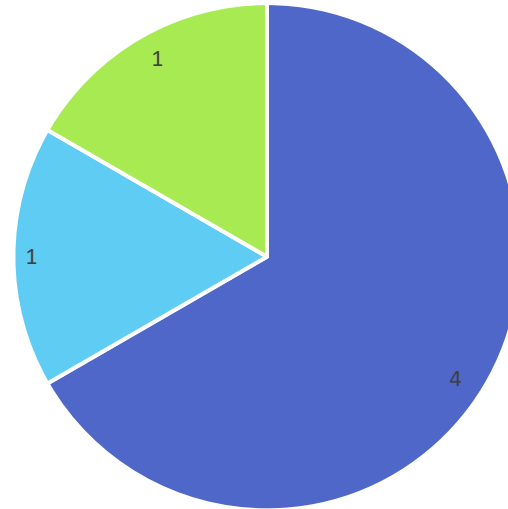
HCT : Association by assay

Association in Elispot



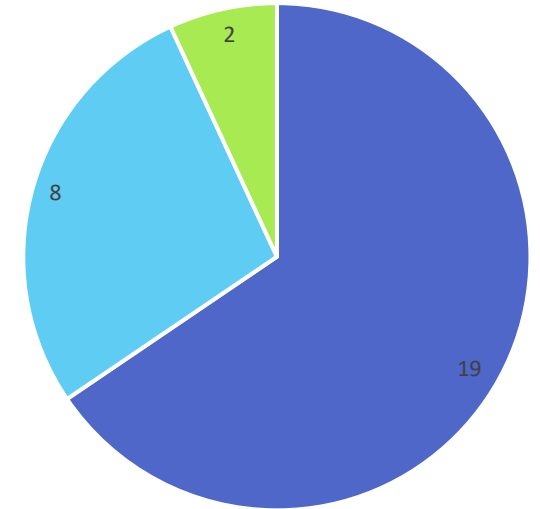
- Significant Positive Response
- Non-Significant Positive Response
- No Response/ Negative Response

Association in QuantiFERON



- Significant Positive Response
- Non-Significant Positive Response
- No Response/ Negative Response

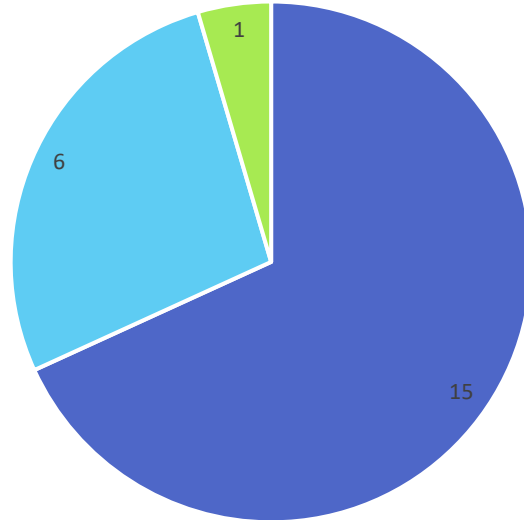
Association in ICS



- Significant Positive Response
- Non-Significant Positive Response
- No Response/ Negative Response

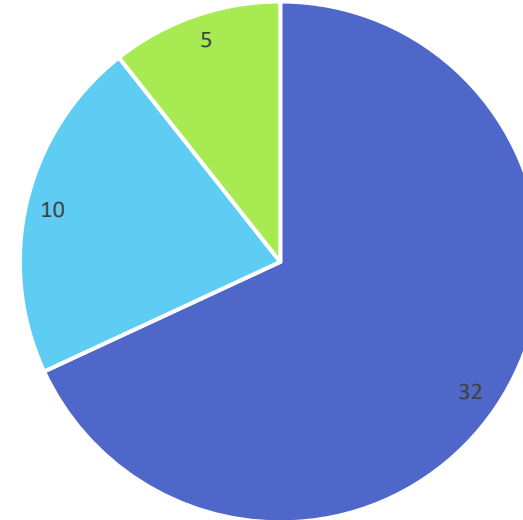
HCT : Association by Serostatus

R+



- Significant Positive Response
- Non-Significant Positive Response
- No Response/ Negative Response

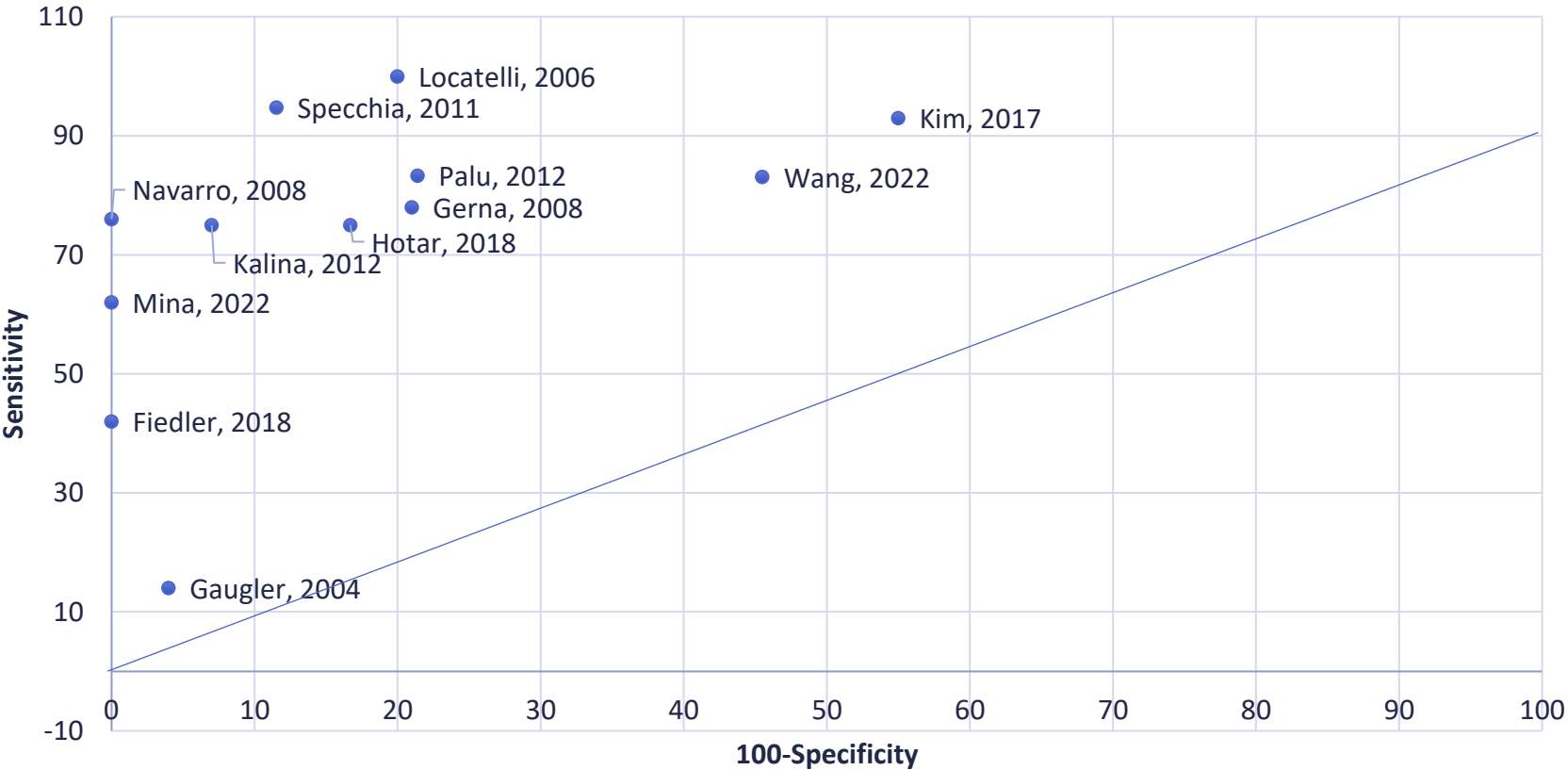
Mixed Serostatus



- Significant Positive Response
- Non-Significant Positive Response
- No Response/ Negative Response

Summary HCT

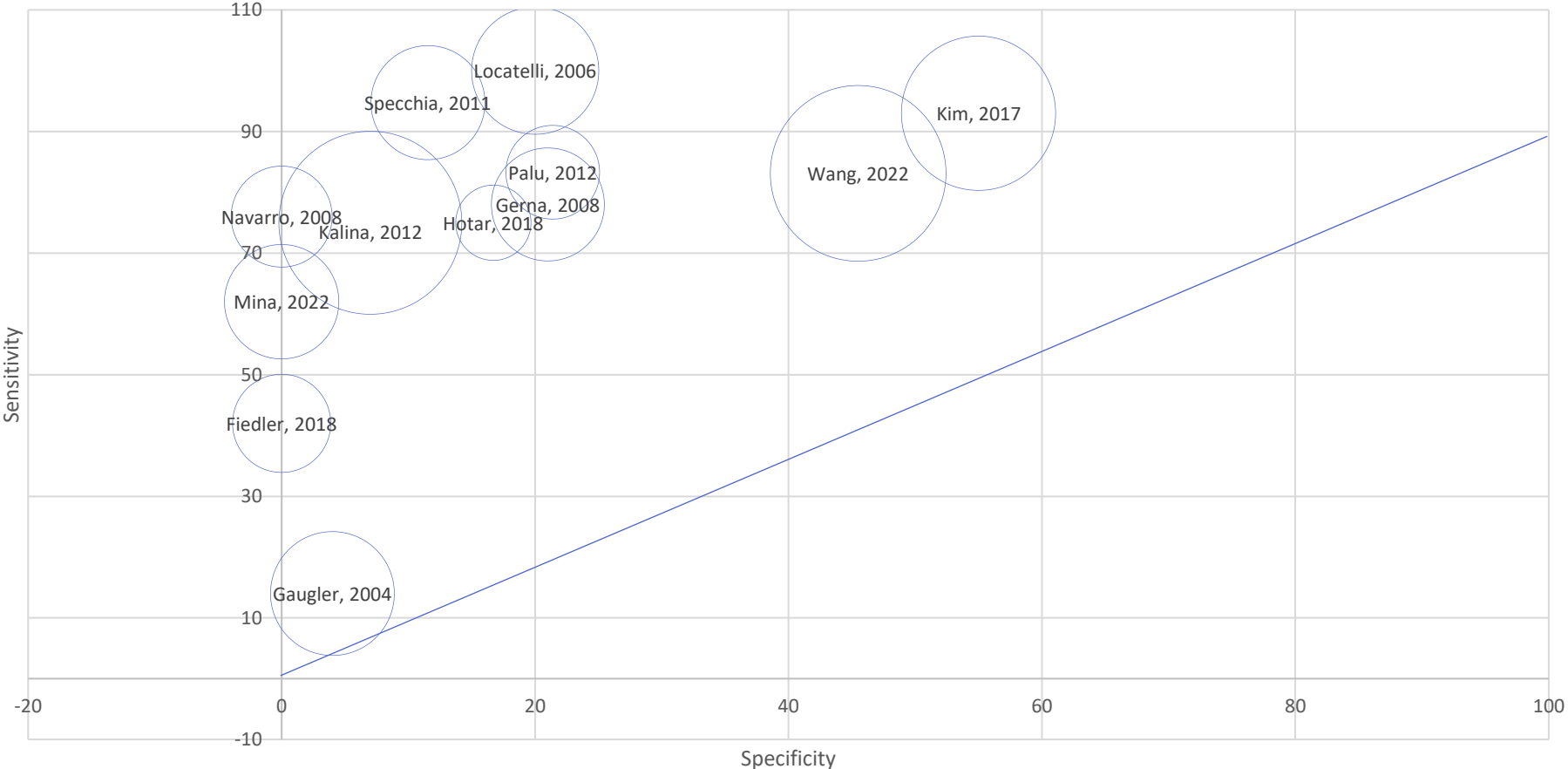
ROC



Selection of studies that self-reported on sensitivity and specificity.

Summary HCT

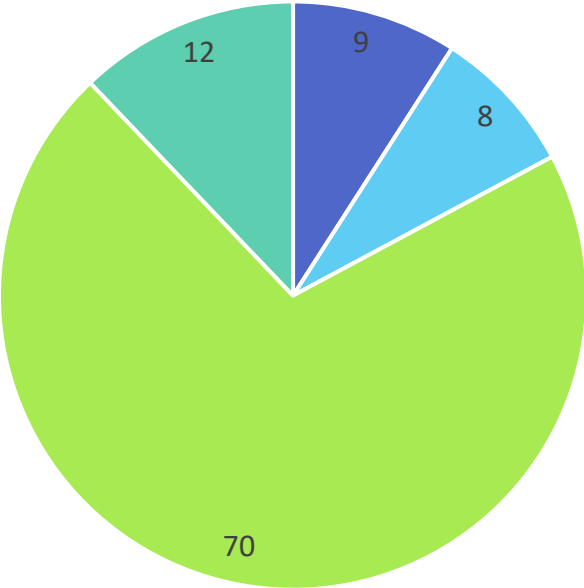
ROC



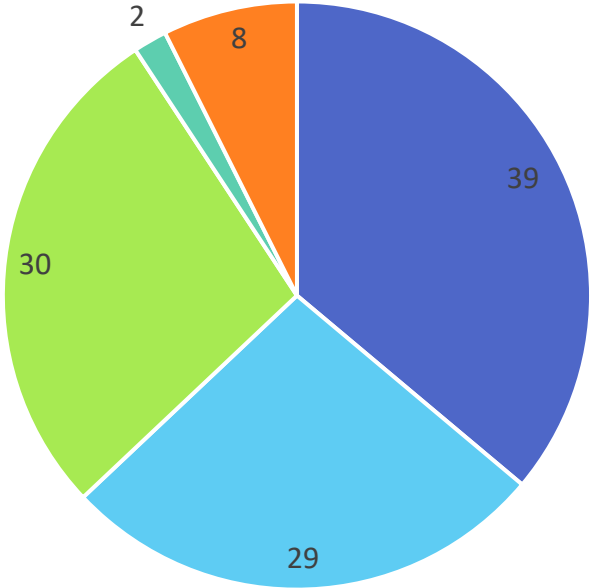
Circle size is proportional to sample size

Summary SOT

Serostatus



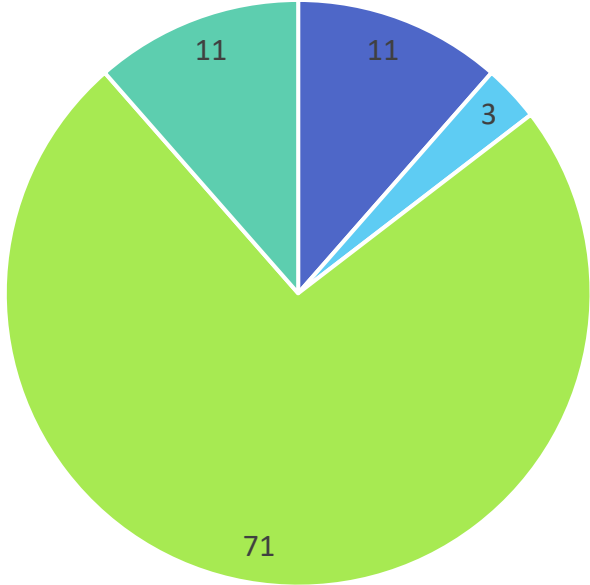
Assay



■ D+/R- ■ D+/R+ ■ mixed ■ unknown ■ Elispot ■ QuantiFERON ■ ICS ■ tetramers ■ others

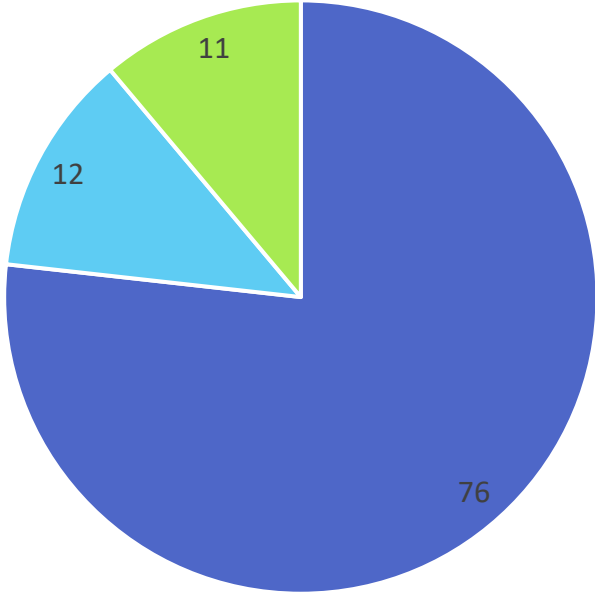
Summary SOT

Timing



- at transplant
- end of prophylaxis
- serial time points
- one time point

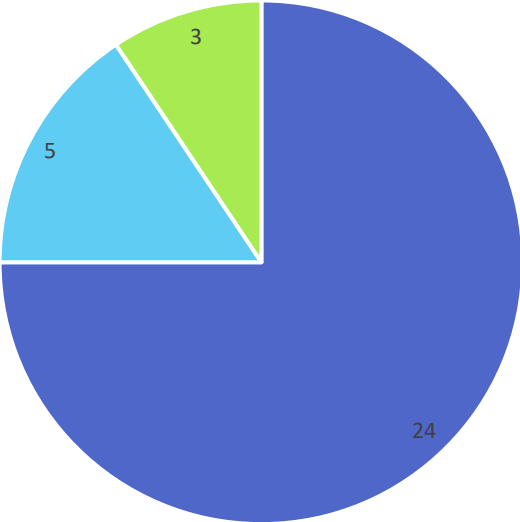
Association



- Significant Positive Response
- Non-Significant Positive Response
- No Response/ Negative Response

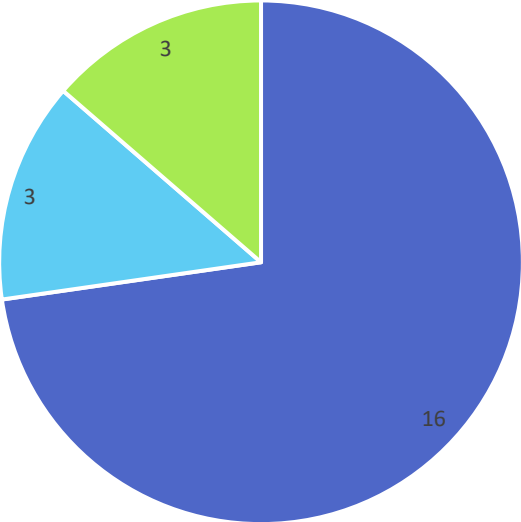
SOT: Association by assay

Association in Elispot



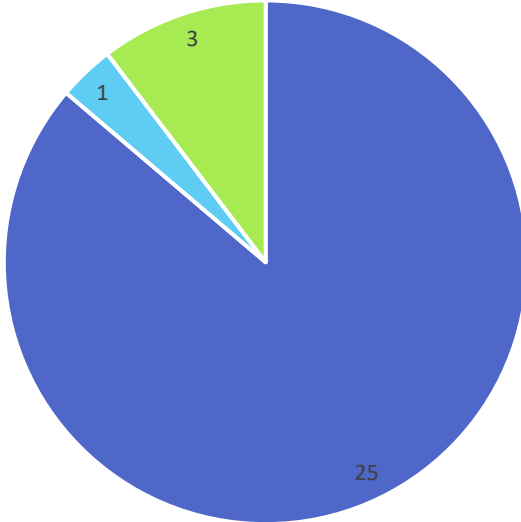
- Significant Positive Response
- Non-Significant Positive Response
- No Response/ Negative Response

Association in Quantiferon



- Significant Positive Response
- Non-Significant Positive Response
- No Response/ Negative Response

Association in ICS

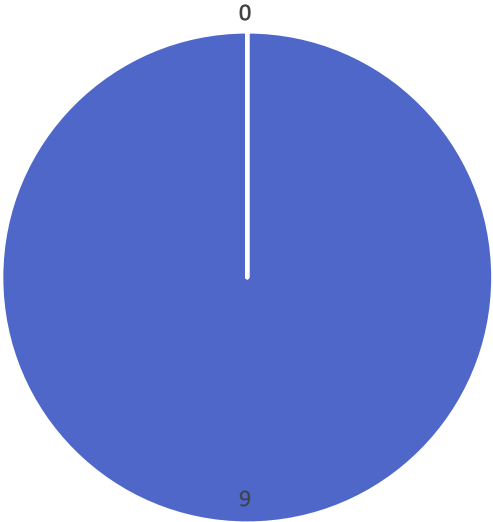


- Significant Positive Response
- Non-Significant Positive Response
- No Response/ Negative Response

SOT: Association by Serostatus

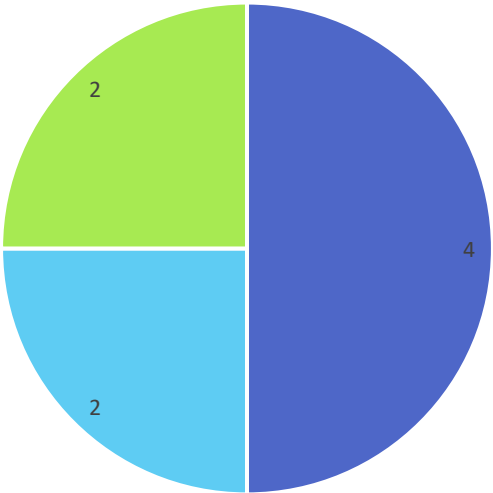


Association in D+/R-



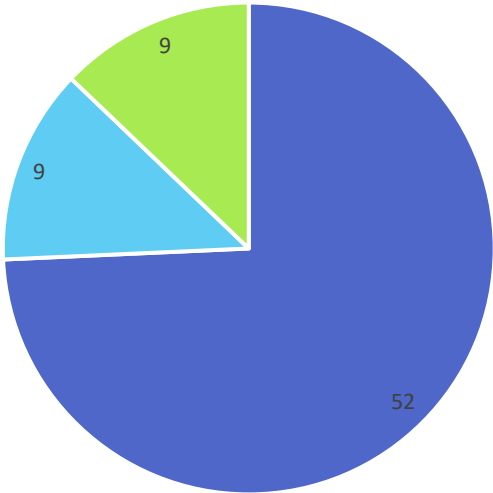
- Significant Positive Response
- Non-Significant Positive Response
- No Response/ Negative Response

Association in D+/R+



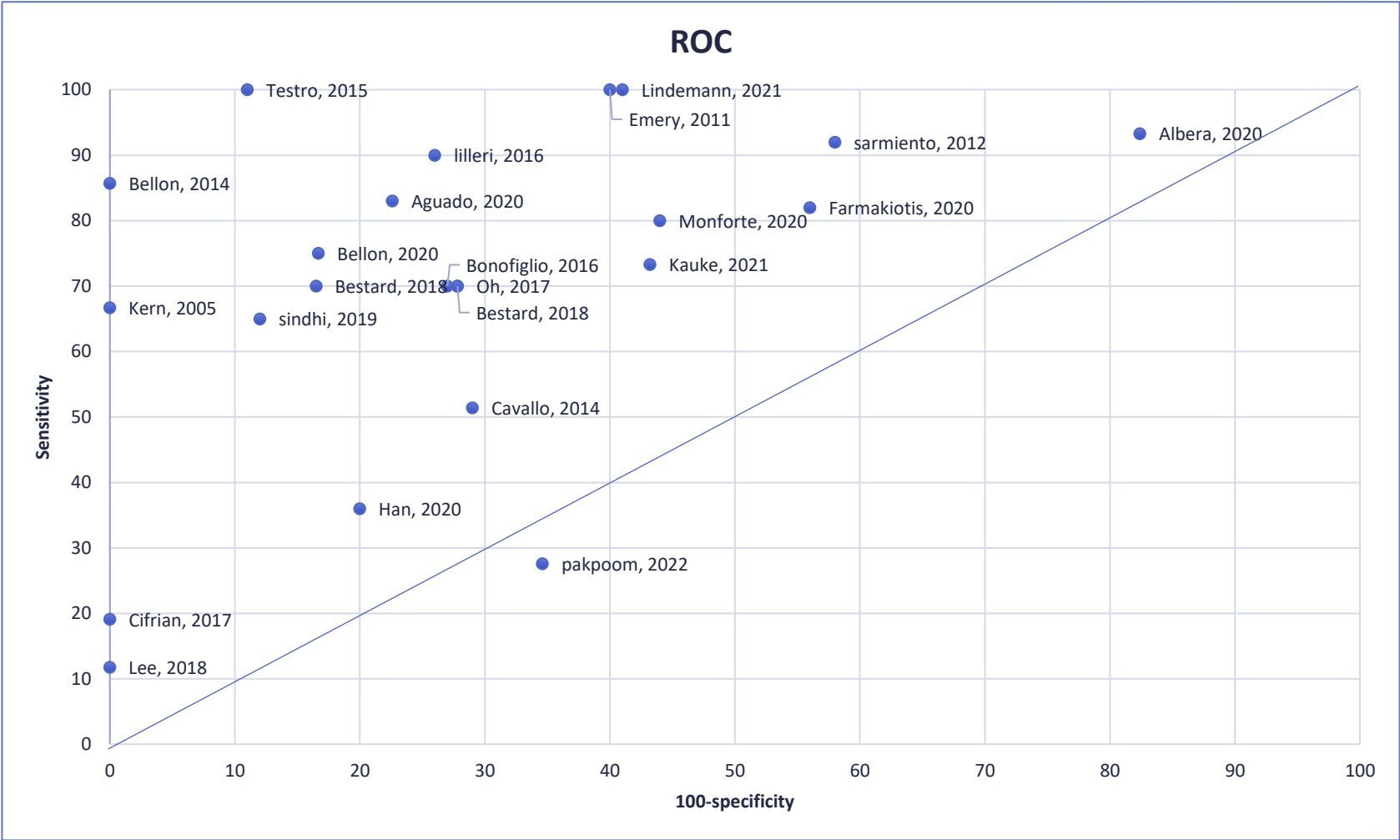
- Significant Positive Response
- Non-Significant Positive Response
- No Response/ Negative Response

Association in mixed serostatus studies



- Significant Positive Response
- Non-Significant Positive Response
- No Response/ Negative Response

Summary SOT



Selection of studies that self-reported on sensitivity and specificity.

Conclusion

HCT:

- The majority of studies are mixed serostatus and use intracellular cytokine staining
- 2/3 show a positive significant association between CMV-CMI and CMV outcomes (with Elispot giving the best results)
- The ROC analysis looks promising

Conclusion

SOT:

- The Majority of studies is mixed serostatus, with Quantiferon, Elispot and ICS being equally represented.
- $\frac{3}{4}$ of studies show a positive association between CMV-CMI and CMV outcomes, with similar results across assays.
- The ROC analysis is positive, but generally inconclusive. More thorough statistical analysis is needed.

Next steps

- **Begin and complete data analysis**
 - Overall question: Can immune monitoring assay predict CMV outcomes?
 - **Prophylaxis:**
 - Can CMV-CMI at transplant (day 1) inform the need for prophylaxis?
 - Can CMV-CMI post-transplant predict optimal duration of prophylaxis?
 - **Infection Prevention:**
 - Can CMV-CMI at the end of prophylaxis predict CMV outcomes?
 - Can CMV-CMI in serial time points predict CMV outcome?
 - Is there an ideal time point?
 - **Antiviral treatment:**
 - Can CMV-CMI inform when to start pre-emptive therapy?
 - Can CMV-CMI inform when to stop treatment?
 - **Pediatrics**

Anticipated Challenges

- Diversity of time points where CMV-CMI was measured
- Diversity of tests
- Diversity in CMV outcome definition

Acknowledgments

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