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UNIVERSITY OF COPENHAGEN

REGION

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Symptomatic CMV Infection Despite Optimal Preemptive CMV Strategy for Recipients of Solid Organ Transplantation and Hematopoietic Stem Cell Transplantation

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on the behalf of the MATCH programme study group

GLOBAL EXCELLENCE IN HEALTH

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Management of Post-Transplant Infections in Collaborating Hospitals

Background

- Cytomegalovirus (CMV) infection frequently complicates the course after solid organ transplantation (SOT) and human stem cell transplantations (HSCT)
- High CMV virus load in the blood compartment has been established as the most prominent risk factor for CMV disease in previous studies[1-3]
- The aim of the pre-emptive strategy is to regularly screen blood in asymptomatic transplant recipients with CMV PCR, and in case of emerging infection then start treatment before CMV disease develops
- However, CMV pneumonitis and gastro intestinal (GI) disease may emerge while blood CMV viral load remains low[3,4]

1. Emery VC et al, Lancet 2000
2. Sia IG et al, JID 2000
3. Razonable RR et al, Clin. Infect. Dis. 2013
4. Cummins NW et al, Transpl. Infect. Dis. 2009

Aim of the study

- To assess the prevalence of CMV disease in an unselected large cohort of patients at the time of diagnosis of the first post-transplant CMV infection in blood

- To identify the main independent risk factor(s) of CMV disease at diagnosis of CMV infection

Patients

- Consecutive SOT and HSCT recipients transplanted from January 2010 to March 2015 and who:
  - Had a known CMV IgG serostatus of donor (D) and recipient (R) at transplantation
    - Possible combinations: D+/R+, D-/R+ or D+/R-
  - Developed a first episode of post transplant CMV infection in the blood compartment within 1 year of transplantation

Study design

- Definition of first CMV infection: 1st of 2 consecutive plasma CMV PCR samples ≥ 300 copies/mL, or 1st ≥ 3,000 cps/mL plasma

- At time of CMV infection, assessment of presence of CMV disease as defined in our hospital:

Certainty:	Type of disease		
	Syndrome	GI disease*	Pneumonia*
Proven	NA	Relevant symptoms + macroscopic lesion + histology	HSCT: pos. CMV PCR in BAL SOT: CMV histology
Probable	SOT: fever, malaise, leukopenia, thrombocytopenia or ALT/AST increase without competing cause(s) identified HSCT: NA	Relevant symptoms+ histology without macroscopic lesions documented	SOT: pos. CMV PCR in BAL
Possible	NA	CMV PCR detected in blood + relevant symptoms+ other probable causes excluded+ adequate response to therapy	CMV PCR detected in blood + relevant symptoms+ other probable causes excluded+ adequate response to therapy

*: relevant symptoms + criteria as indicated; sub grouped according to presence possible additional/competing cause(s) (for GI also incl. GvHD)

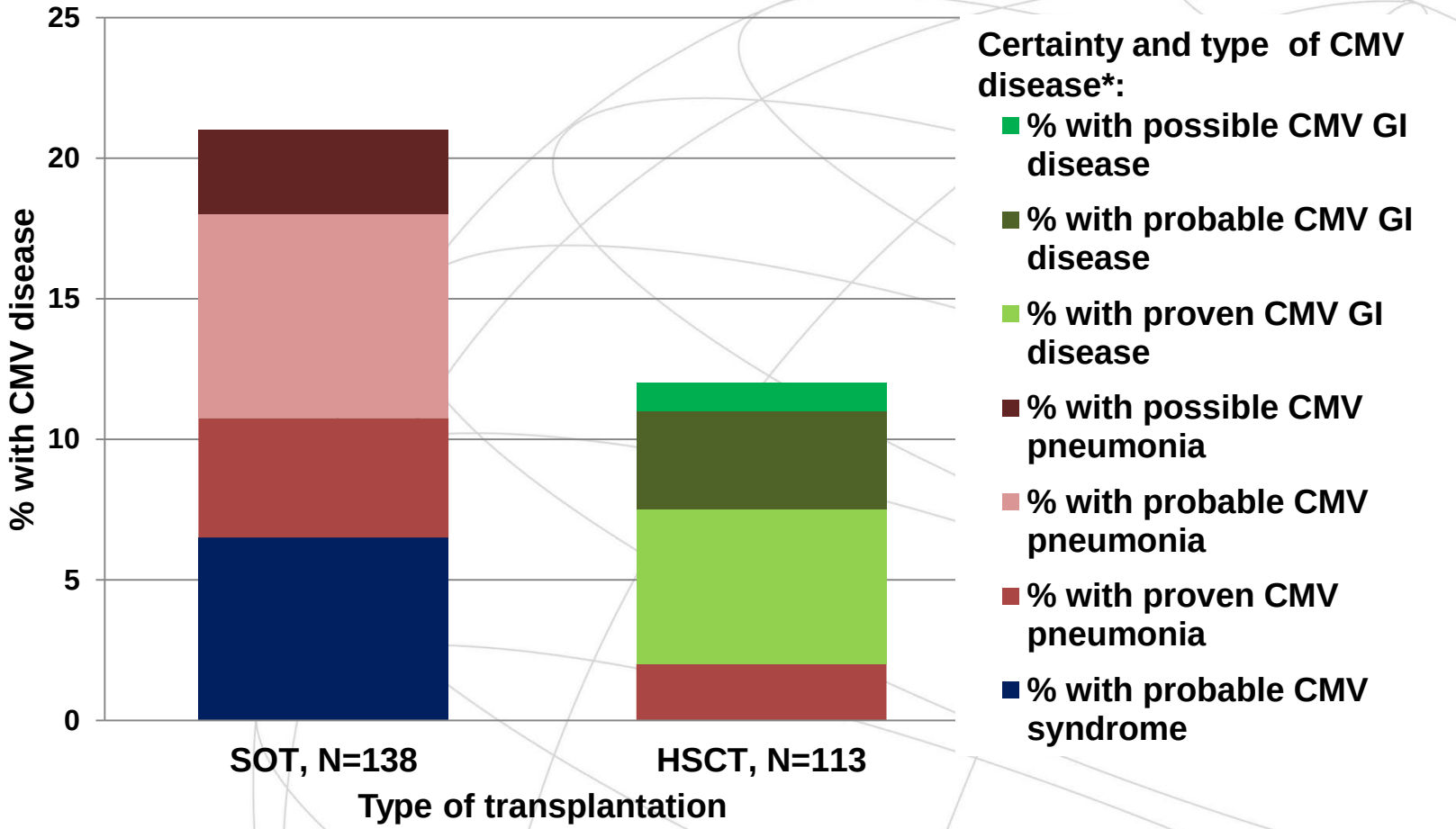
Statistical analysis

- Standard descriptive statistics
- Risk factors for CMV disease were explored using univariate and multivariate logistic regression adjusted for relevant confounders

Characteristics of included recipients

- 251 recipients (138 SOT; 113 HSCT) was diagnosed with first-time CMV infection in blood
- Demographics, and CMV risk factor profiles were comparable between transplant type
  - CMV infection developed later in SOT due to use of primary chemoprophylaxis than in HSCT
- Conversely, prevalence and type of CMV disease at diagnosis of CMV infection differed:

Prevalence and type of CMV disease at first CMV infection in SOT and HSCT recipients



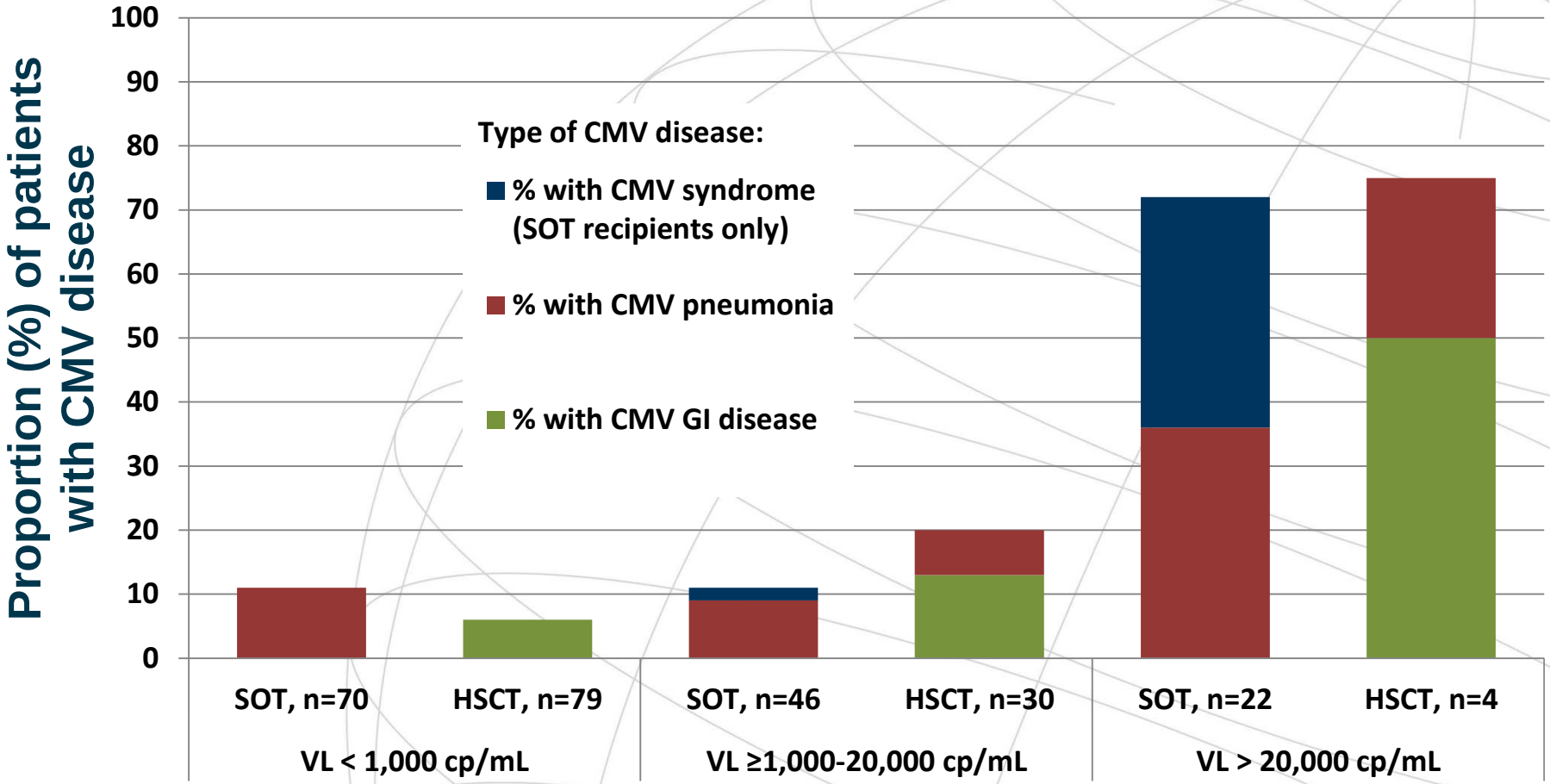
***No other types of organ disease was observed**

Competing causes: Per definition none were observed for CMV syndrome and possible cases of organ disease.

SOT: CMV pneumonia (0/6 of proven and 4/10 of probable cases (4/4 pulmonary fungal infection and all had high CMV PCR in BAL).

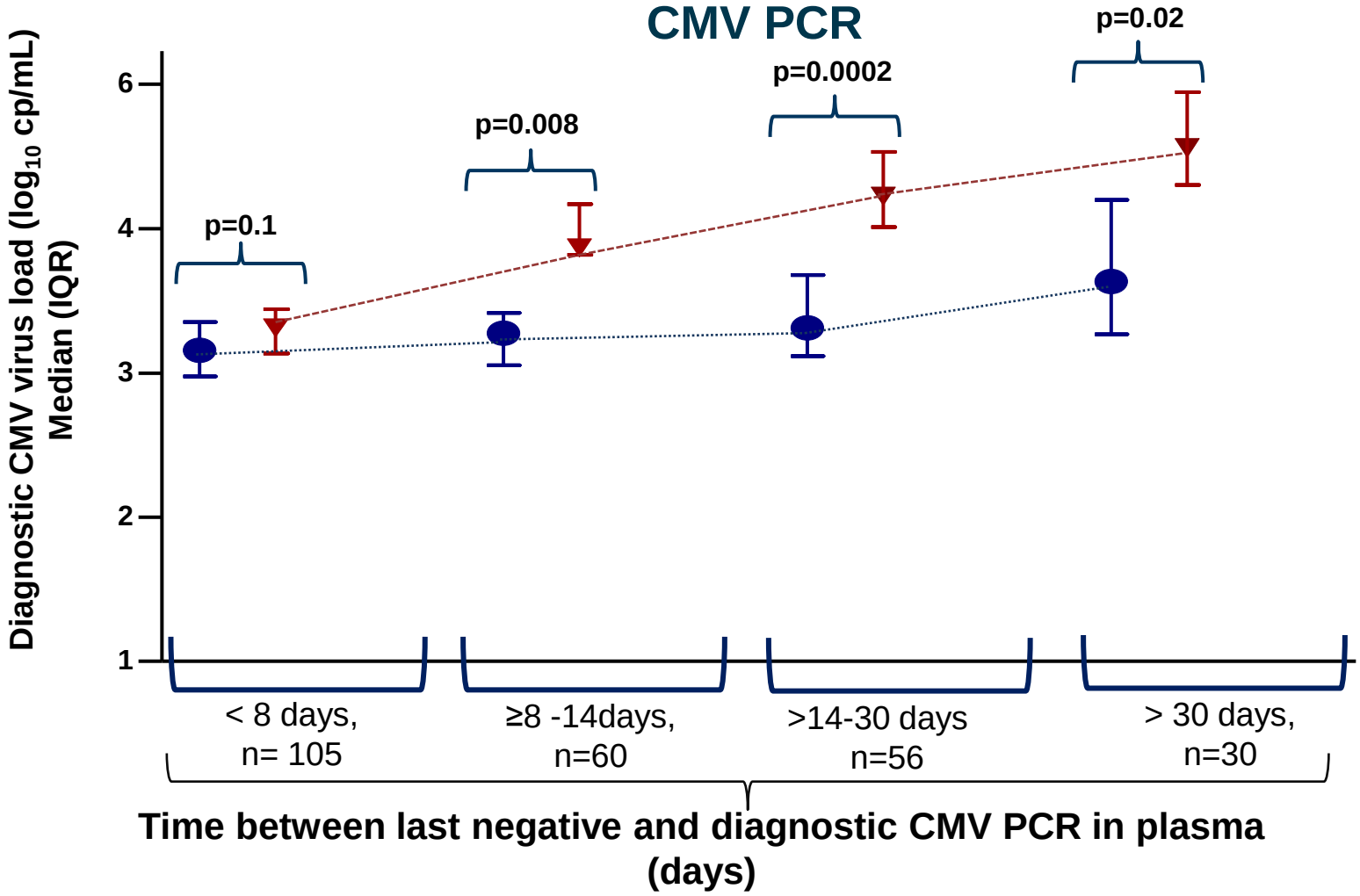
HSCT: 3/3 proven CMV pneumonia had competing causes (fungal and influenza). Among 6 proven GI disease 3/6 had GvHD & 1/6 had competing cause (adenovirus); among 4 probably cases, 1/4 had GvHD, and 1/4 had competing cause (*C. diff*).

Prevalence of CMV disease (by type) according to diagnostic virus load at first CMV infection in SOT and HSCT recipients



Virus load (VL) of the diagnostic CMV PCR in plasma

Diagnostic viral load with and without CMV disease and prevalence of CMV disease according to time between last negative and diagnostic CMV PCR



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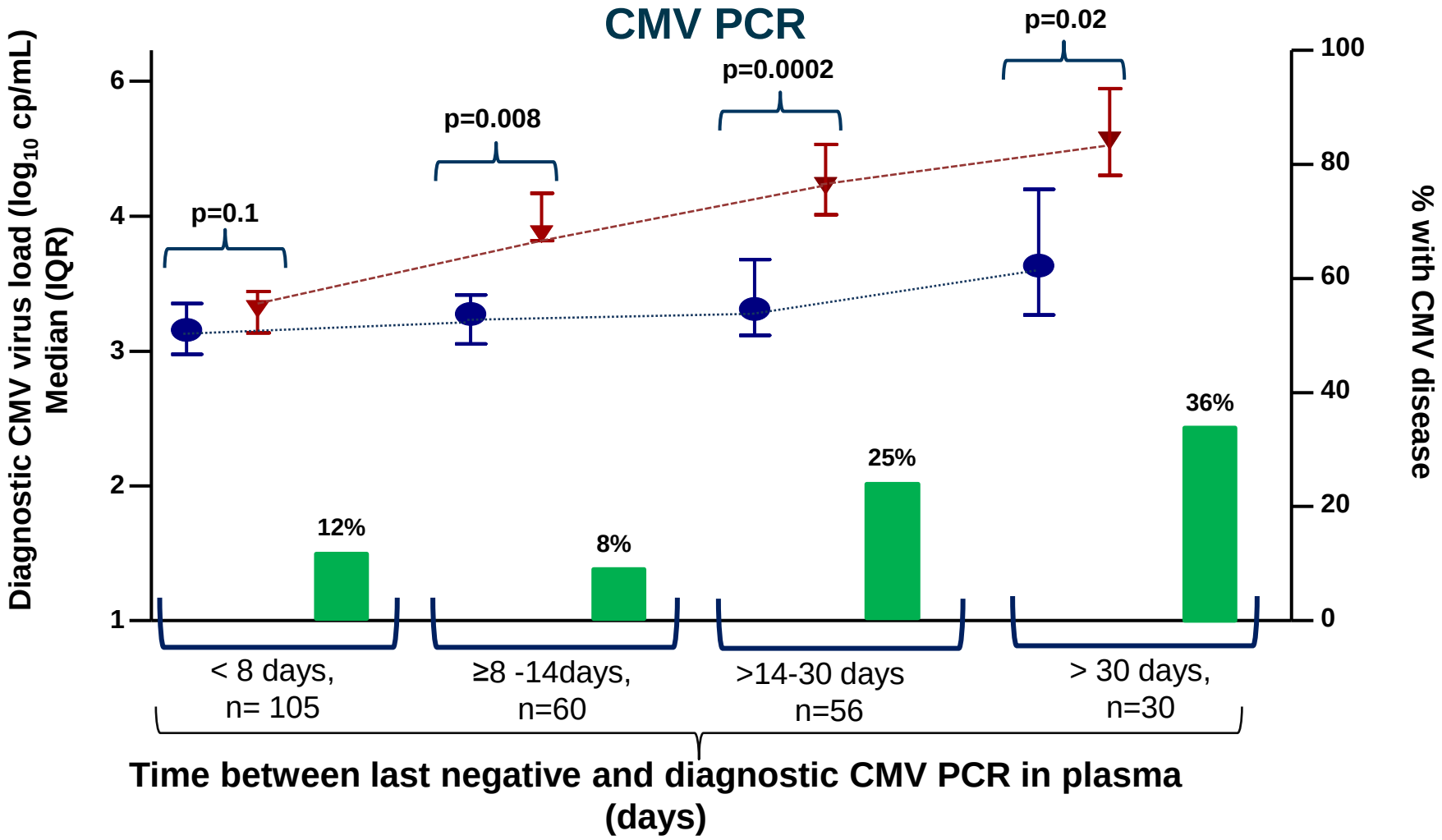
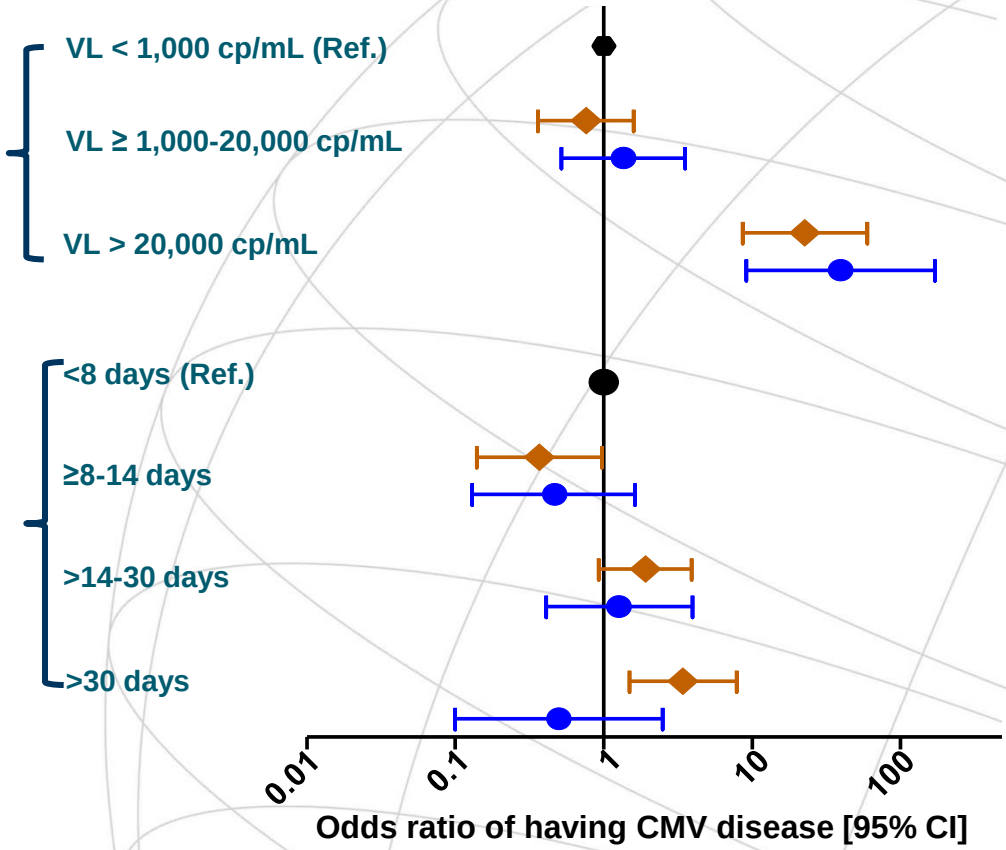


Odds (unadjusted and adjusted) of CMV disease for two main factors associated with CMV disease



	Odds ratio [95% CI]	p-value
VL < 1,000 cp/mL (Ref.)	Ref.	
VL ≥ 1,000-20,000 cp/mL	0.76 [0.36-1.59]	0.46
	1.36 [0.52-3.55]	0.54
VL > 20,000 cp/mL	22.7 [8.67-59.6]	<0.0001
	39.6 [9.16-171.5]	<0.0001
<8 days (Ref.)	Ref.	
≥8-14 days	0.37 [0.14-0.98]	0.04
	0.47 [0.13-1.63]	0.23
>14-30 days	1.91 [0.93-3.93]	0.08
	1.27 [0.41-3.98]	0.68
>30 days	3.42 [1.49-7.86]	0.004
	0.50 [0.10-2.50]	0.40

◆ Unadjusted
● Adjusted*

*Logistic regression model adjusted for age, gender, type of transplantation, risk of CMV infection according to donor/recipient CMV IgG serostatus, and year of transplantation

Conclusion

- High virus load at the time of diagnosis of CMV infection in blood is the main risk factor for CMV disease
  - Patients screened with > 2 weeks interval had higher diagnostic viral load and elevated risk of CMV disease
  - Hence, interval between blood CMV PCR screening should not excess 2 weeks while transplant recipients are at high risk of CMV infection when applying a pre-emptive strategy to reduce risk of CMV disease

- Despite recommended weekly/biweekly CMV PCR screening interval, around 10% of transplant recipients (irrespective of type of transplantation) had CMV disease at diagnosis of their first CMV infectious episode
  - Type of disease: CMV pneumonia or GI disease
  - This observation provides a rationale for further studies focusing on lung recipients (prolongation of duration of primary chemoprophylaxis) and HSCT recipients (use of brincidofovir as primary chemoprophylaxis)

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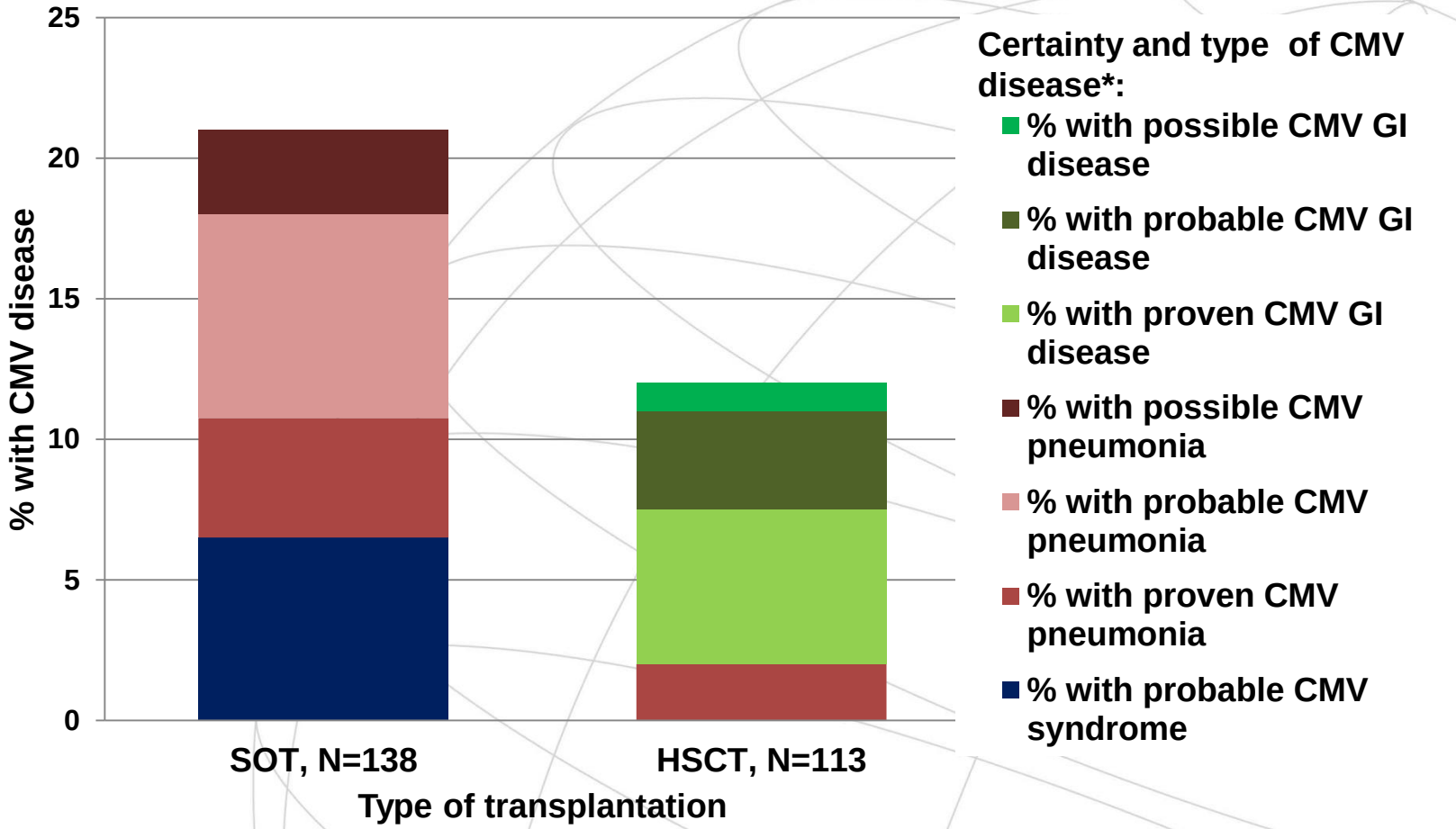
Prevalence and type of CMV disease at first CMV infection in SOT and HSCT recipients



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