Single High-dose of Liposomal Amphotericin B in HIV/AIDS-related Disseminated Histoplasmosis: a Randomized Trial

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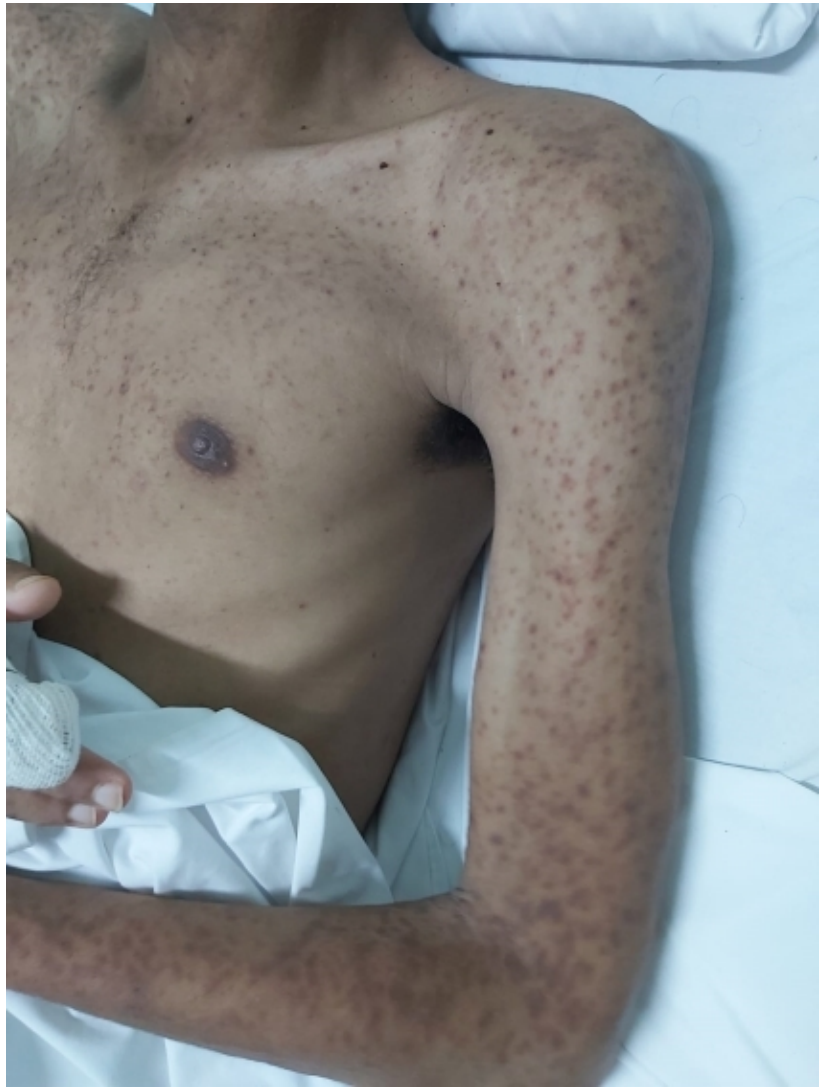
In collaboration with Gilead Sciences and IMMY

Late Breaker Abstract – ID Week – Oct 2022

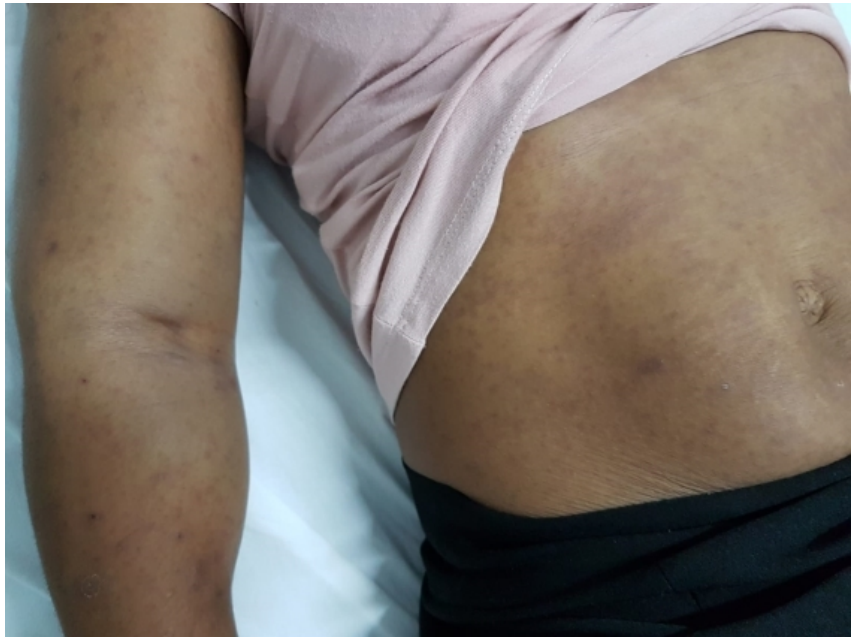
Rationale

- Disseminated histoplasmosis is a major killer of PLWHA.



Rationale

- Disseminated histoplasmosis is a major killer of PLWHA.
- In developing countries, many patients are treated with high doses of Amphotericin B (AmB) deoxycholate for 2-6 weeks.



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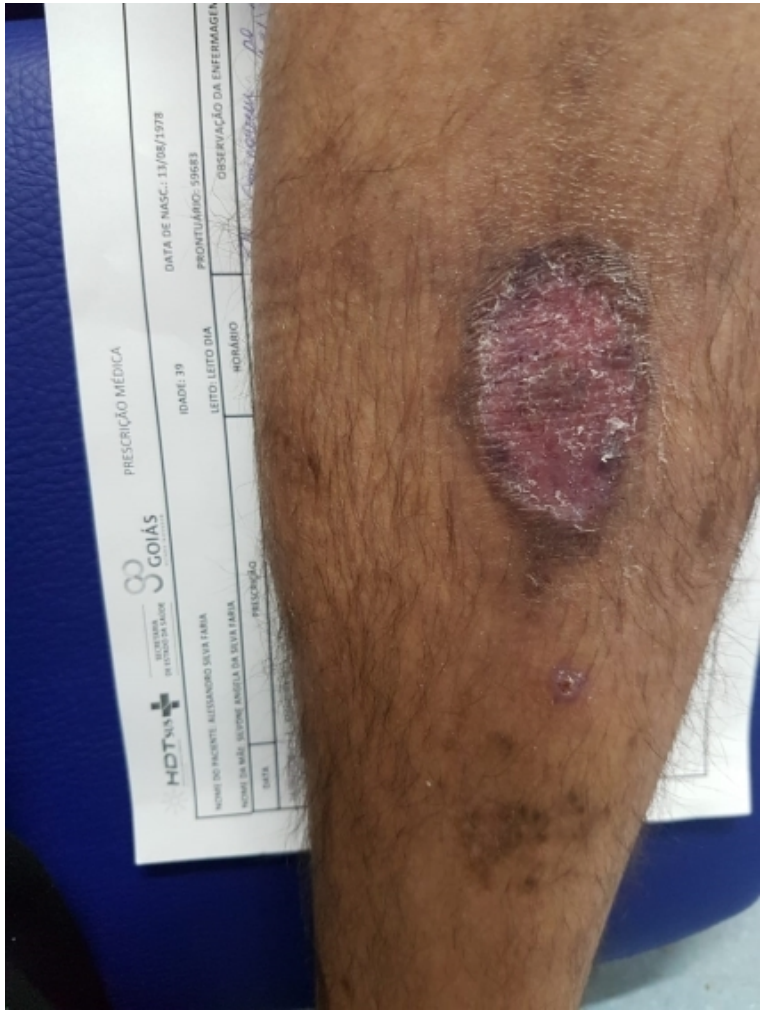
- This has never been studied in histoplasmosis.



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- **Induction therapy** for disseminated histoplasmosis:
  - ✓(i) 10 mg/kg single IV dose of Liposomal Ampho B (L-AmB);
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- Itraconazole capsules 400 mg/daily for 1 year for all

Exclusion criteria

- Previous diagnosis of histoplasmosis.
- Pregnant or lactating women.
- Renal insufficiency (serum creatinine and urea > 1.5x the upper limit of normal).
- Patients who have received more than one dose of a polyene antifungal in the last 48 hours.
- Patients diagnosed with histoplasmosis that affect the central nervous system.
- Patients who, at the trial of the attending physician, are expected to die within 48 hours.
- Patients diagnosed with tuberculosis.
- Patients with any disease or condition that, in the opinion of the investigator, may interfere with the assessments or participation in the study.

Primary endpoint

- **Clinical response D14**
  - ✓Resolution of fever AND signs / symptoms attributable to histoplasmosis

Secondary endpoints

- Overall mortality D14
- Renal function abnormalities

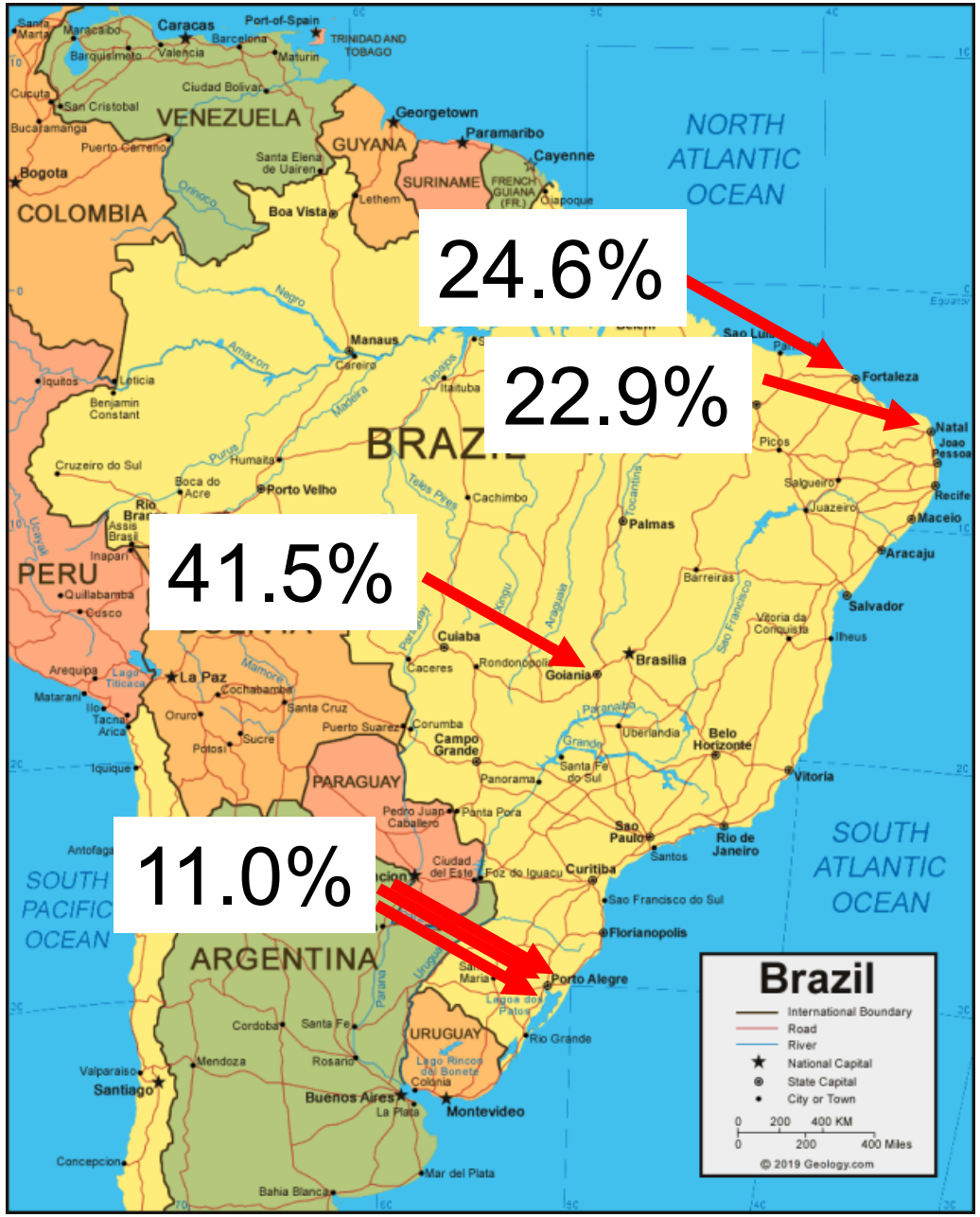
Determination of kidney toxicity (KDIGO guidelines 2012)

Table 2 | Staging of AKI

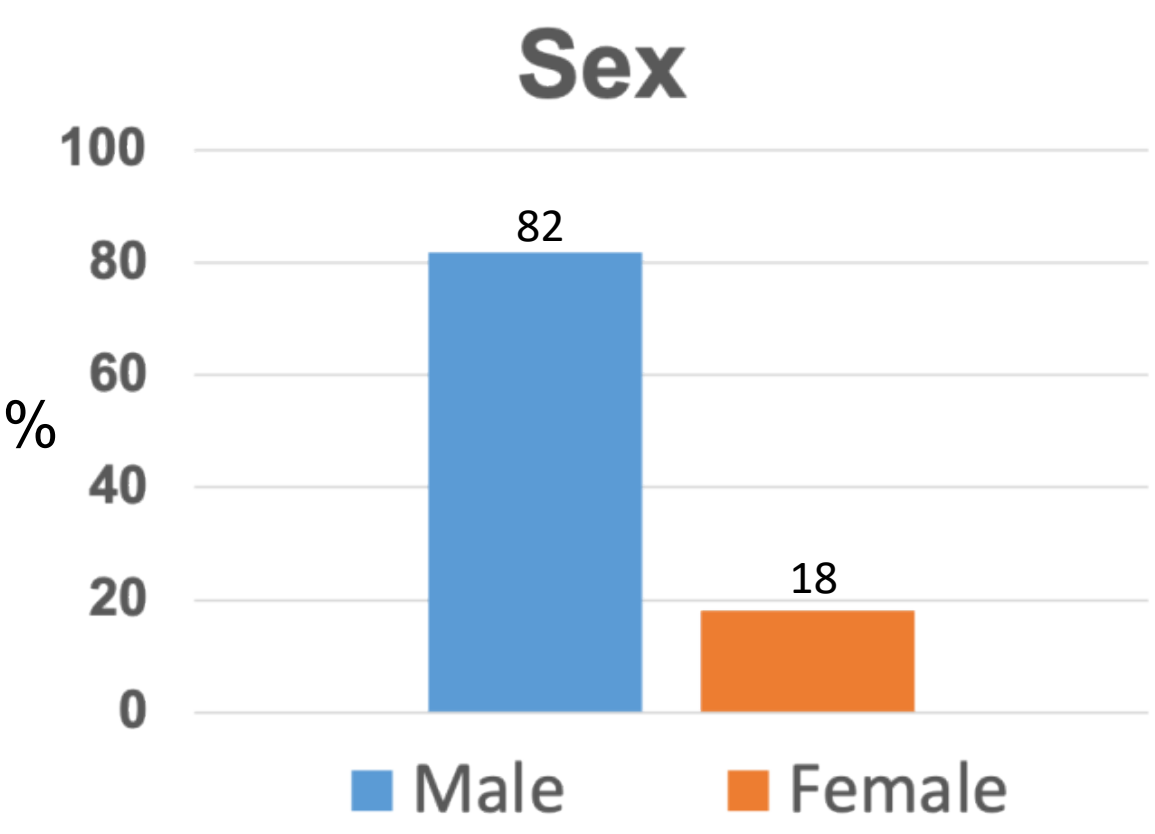
Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ⩾0.3 mg/dl (⩾26.5 μmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ⩾12 hours
3	3.0 times baseline OR Increase in serum creatinine to ⩾4.0 mg/dl (⩾353.6 μmol/l) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ⩾24 hours OR Anuria for ⩾12 hours

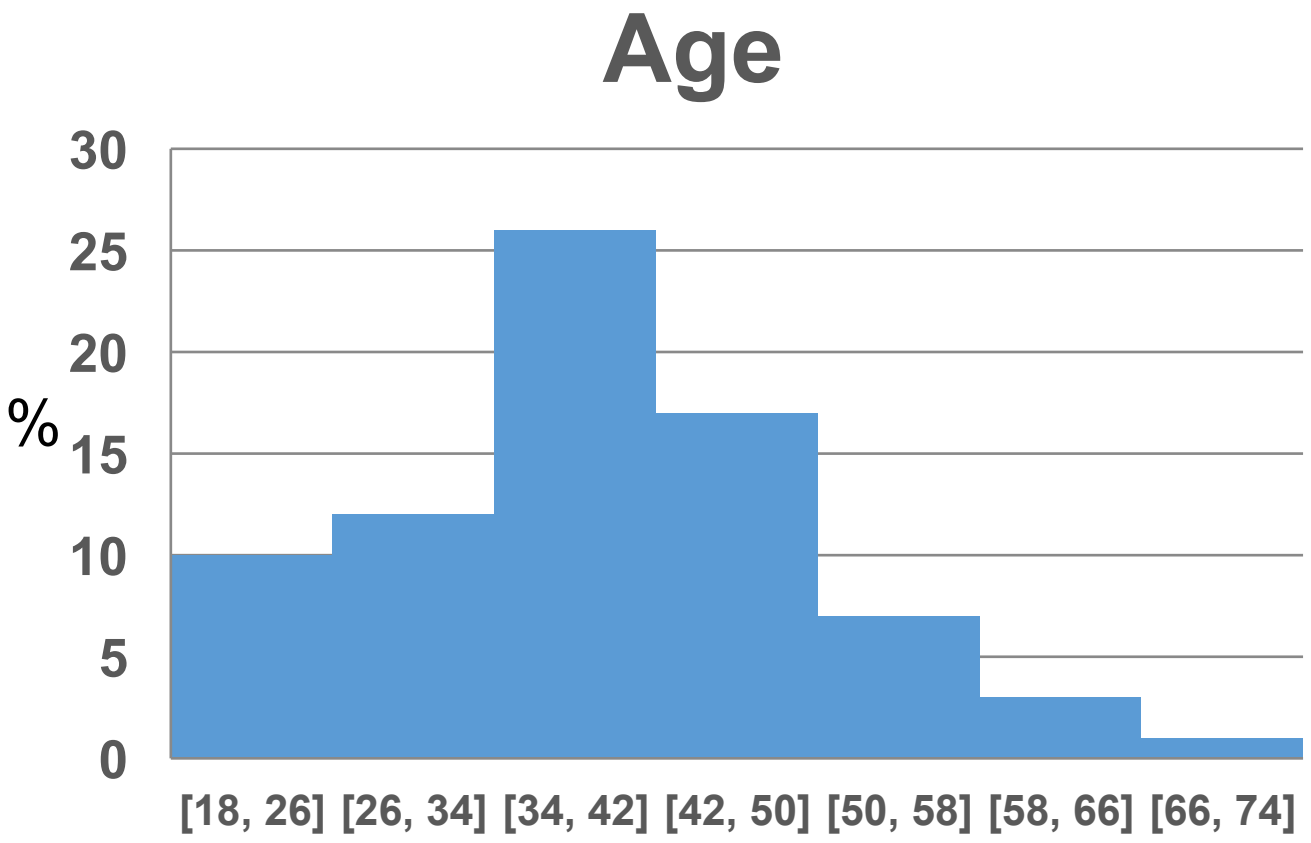
Results

- Aim: 99 patients
- 247 patients screened, **118 were randomized**
- 6 medical centers in Brazil



Baseline characteristics

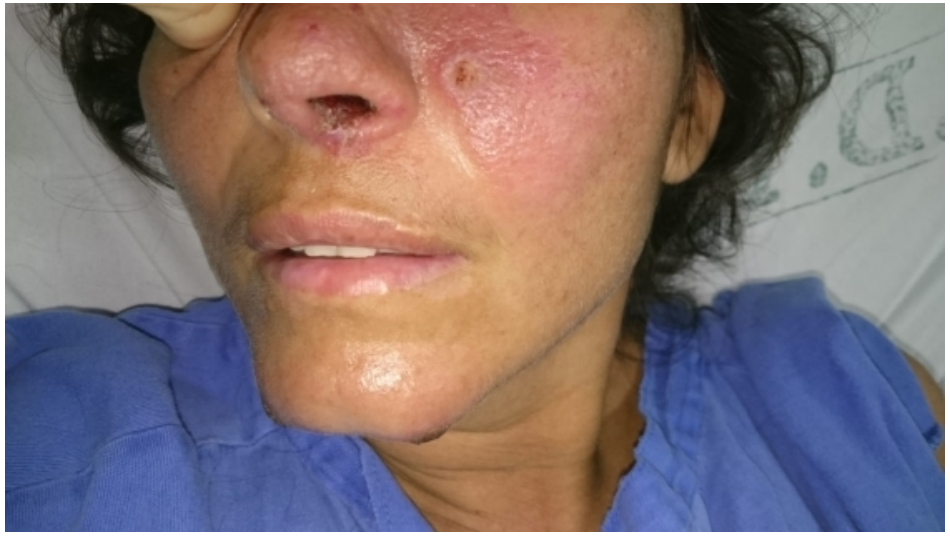




Median 38.0 yrs-old (range, 18-74)

Regarding HIV status

- **First AIDS presenting disease** for 51%



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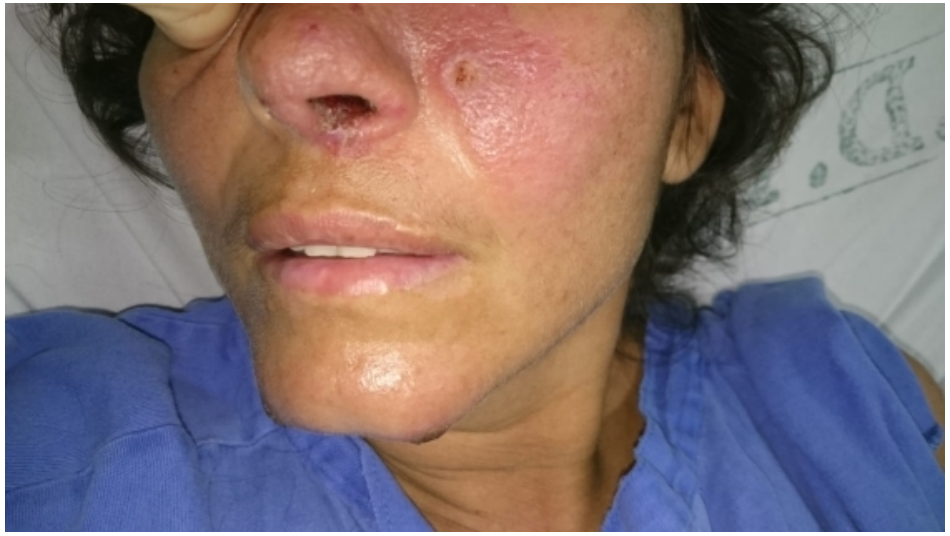
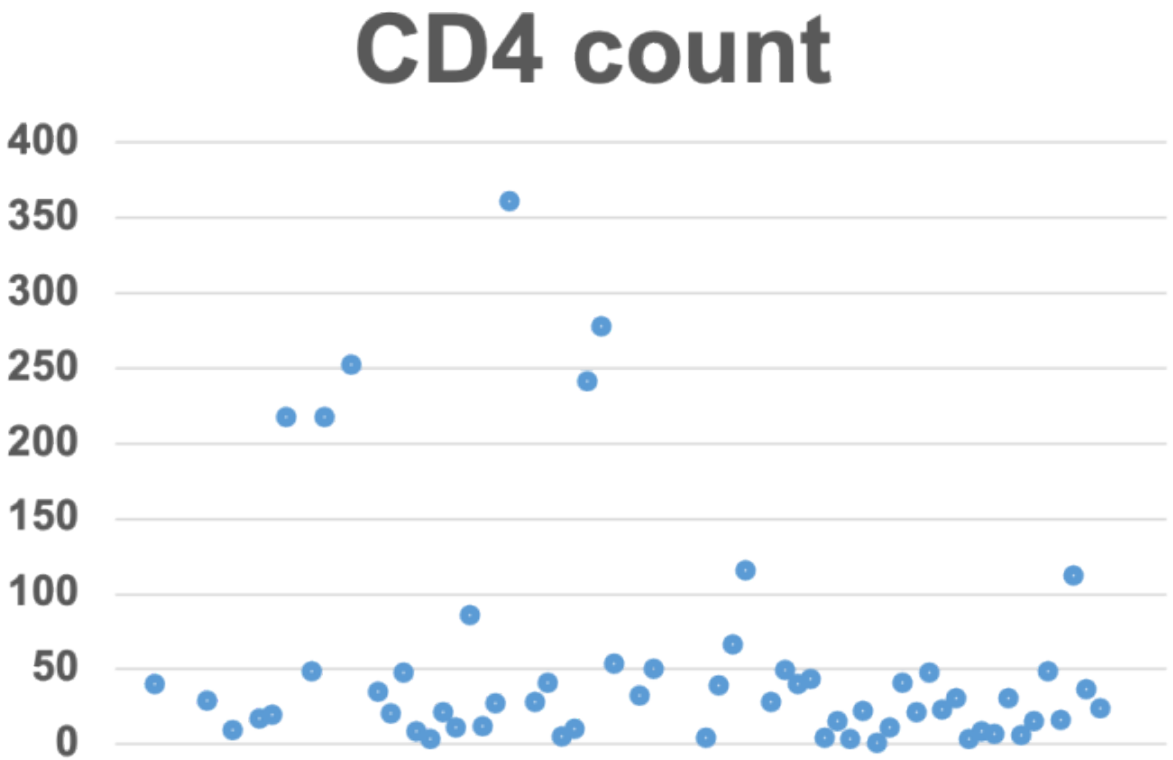




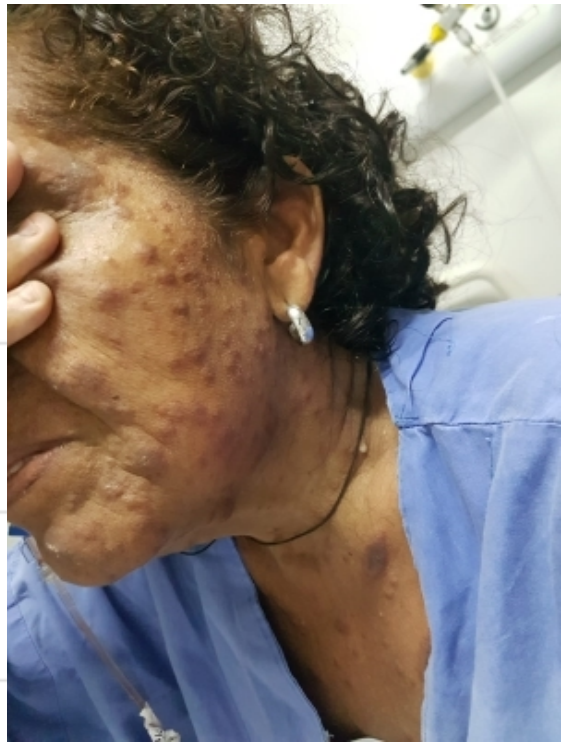
Median CD4 = 25 cells/μL (range, 1-361)

HIV viral load

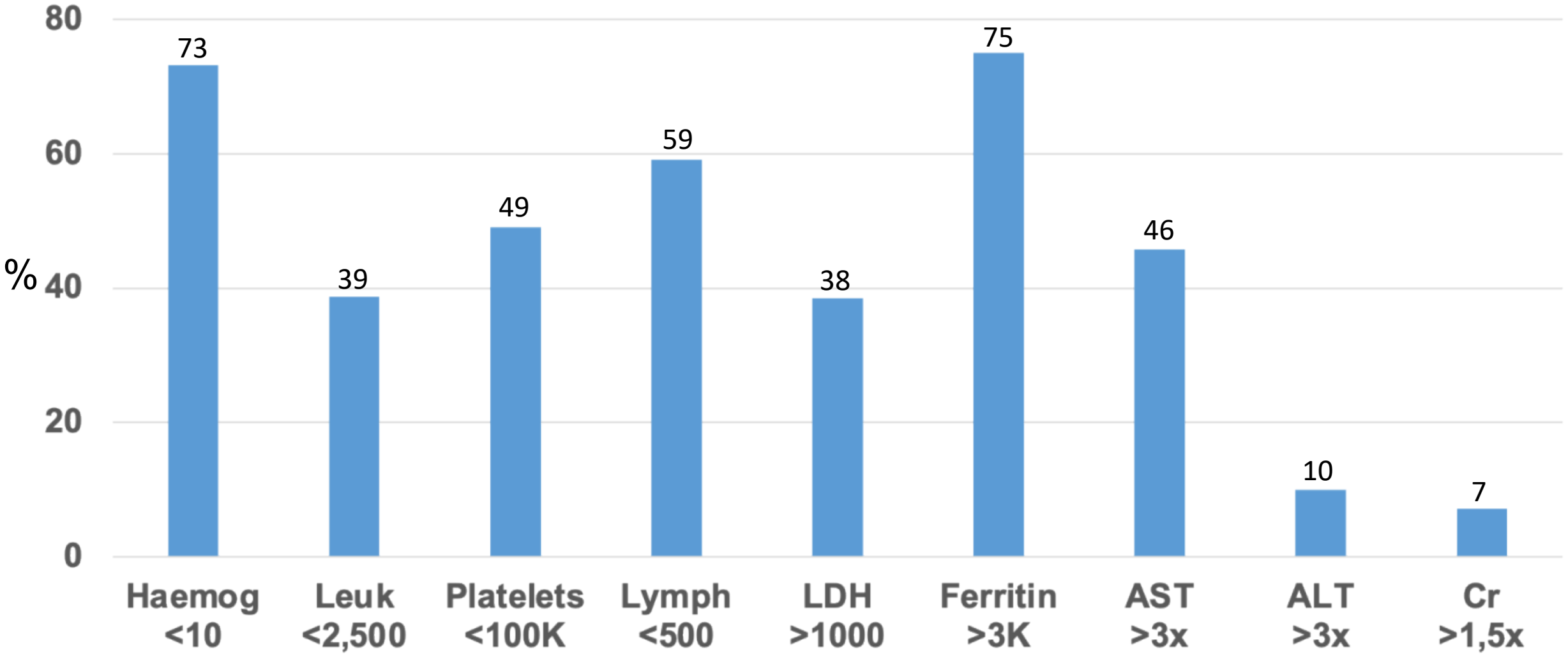
Median = 5.56 $\log_{10}$ copies/mL

(range, 1.6-7.1)

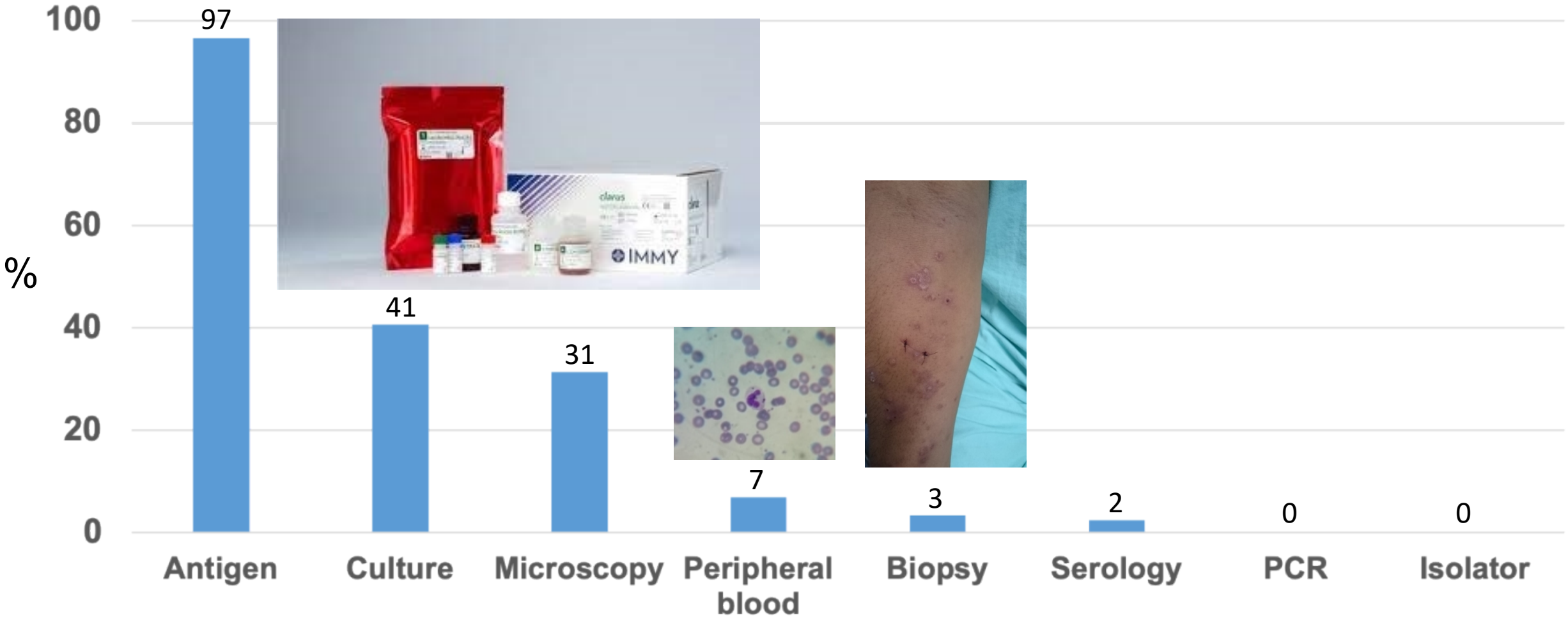
Clinical findings



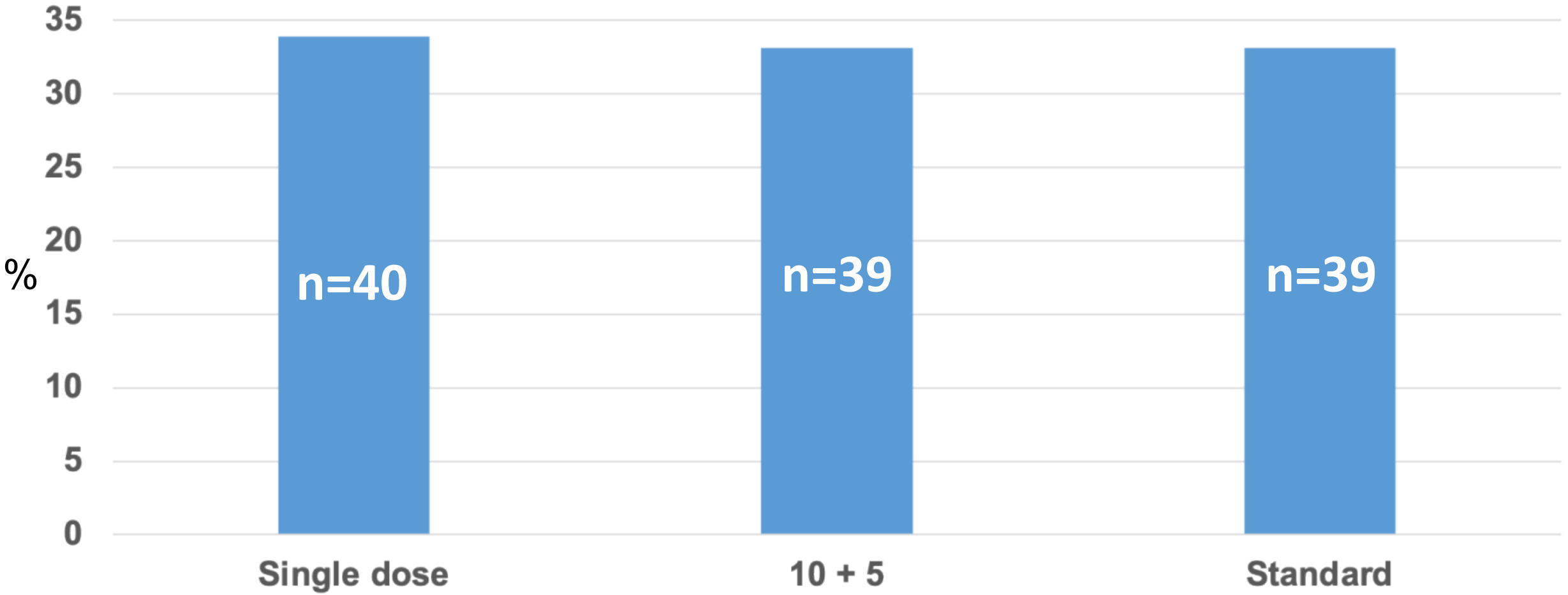
Main lab abnormalities at baseline



Diagnostic methods



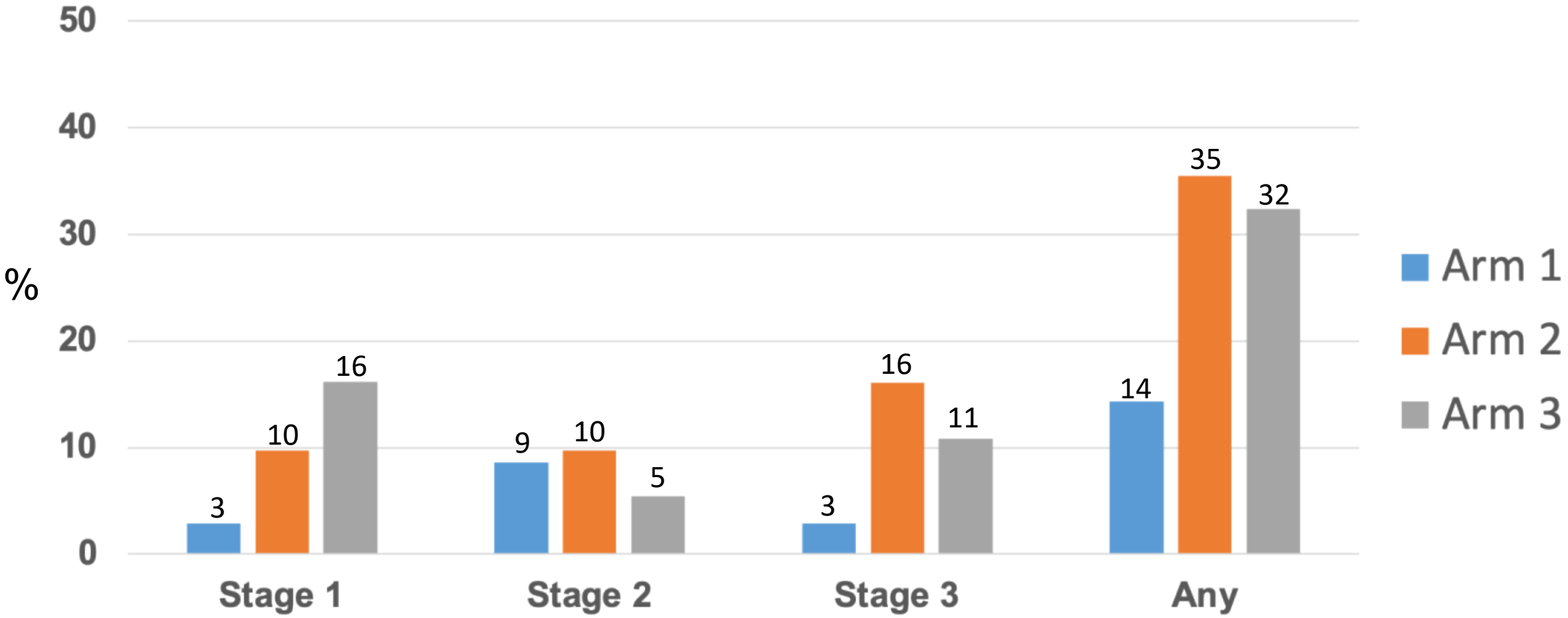
Randomization arms



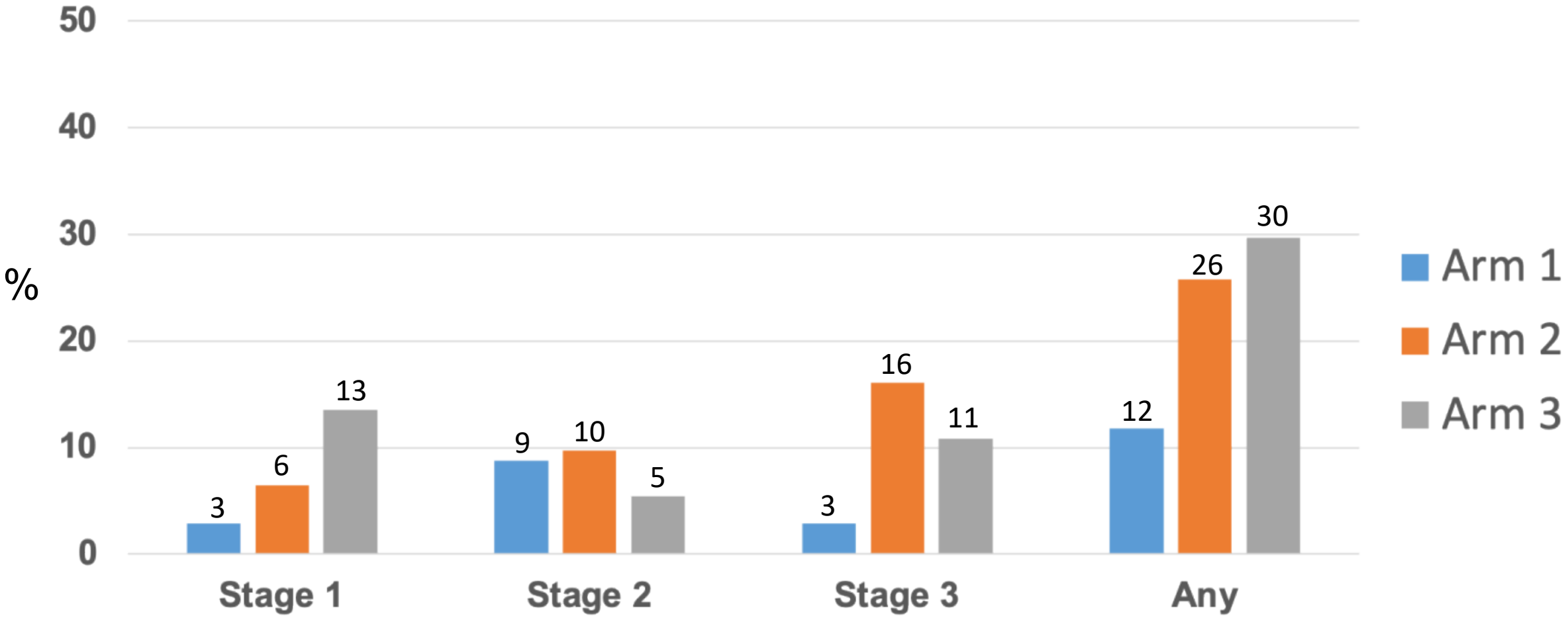
	Arm 1 (10 mg/kg)	Arm 2 (10+5 mg/kg)	Arm 3 (3 mg/kg/d controls)
Age (median)	40	39	39
Male sex	88%	72%	87%
CD4 count (median)	27	27	22
Viral load, $\log_{10}$ (median)	5.3	5.2	5.6
Histo antigen, EIV (median)	47.6	30.7	31.0
Karnofsky Score $\leq$70	52%	49%	51%
Fever (%)	70%	58%	69%
Weight loss (%)	80%	56%	74%
Oral lesions (%)	42%	33%	31%
Skin lesions (%)	42%	31%	41%

Baseline Lab Value	Arm 1 (10 mg/kg)	Arm 2 (10+5 mg/kg)	Arm 3 (3mg/kg/d controls)
Haemoglobin (median)	8.80	9.10	9.35
Leukocytes (median)	2,930	3,030	2,850
Neutrophils (median)	2,025	2,363	2,285
Lymphocytes (median)	443	313	431
Platelets (median)	90,000	135,000	93,000
Creatinine (median)	0.80	0.78	0.77
LDH (median)	496	618	691
Ferritin (median)	5,193	8,250	8,250
AST (median)	43	102	88
ALT (median)	43	58	59

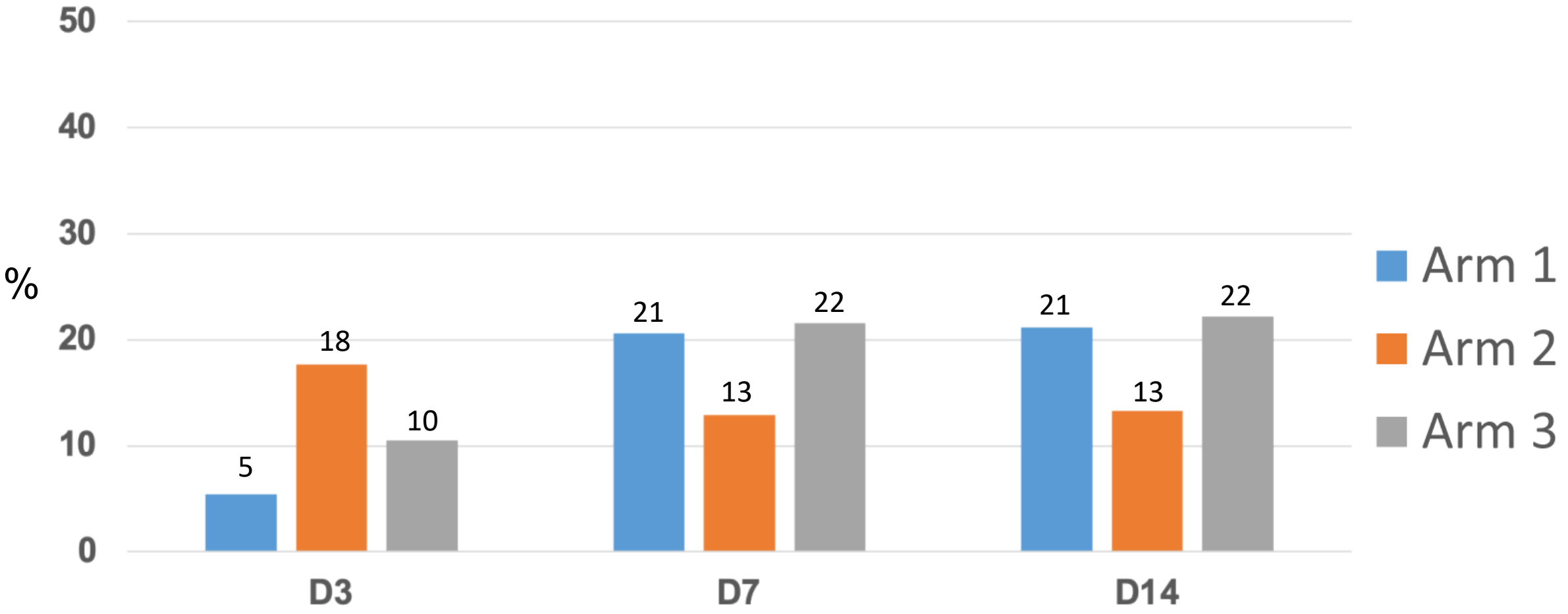
Kidney toxicity Day 7



Kidney toxicity Day 14



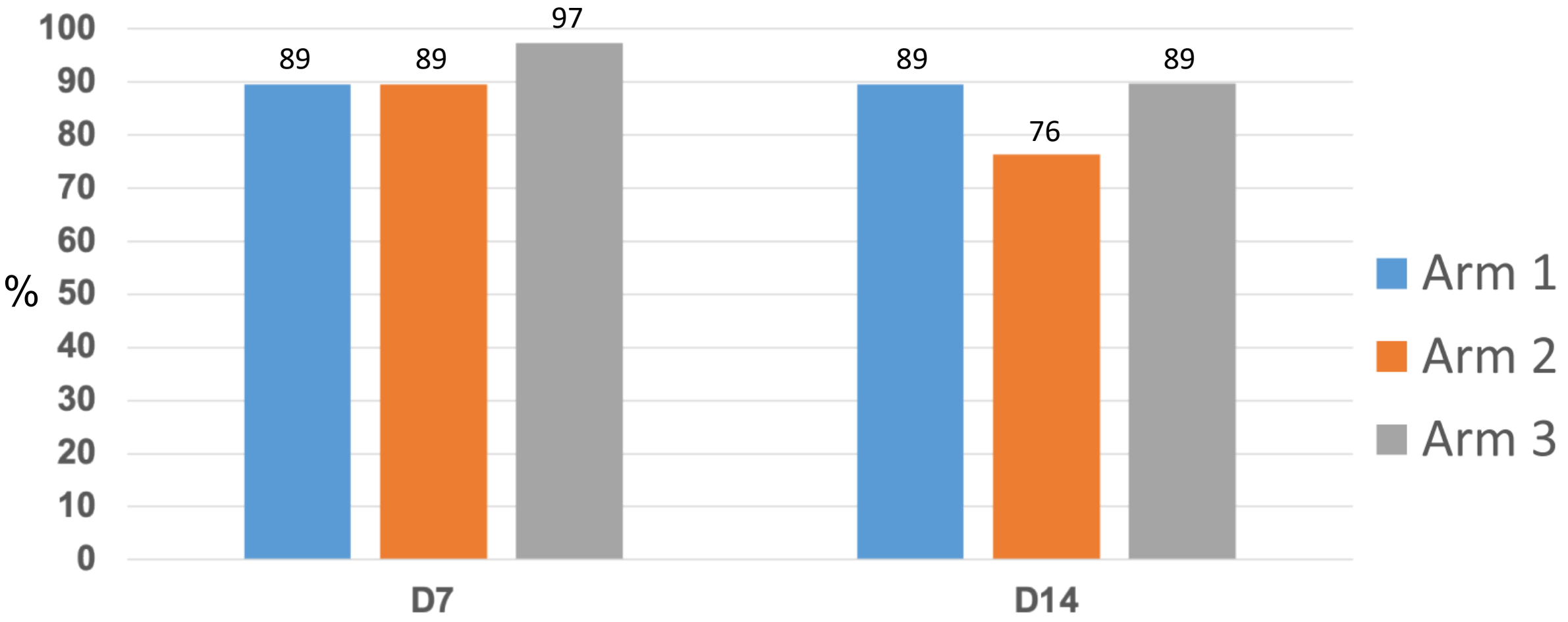
Haemoglobin drop ≥2g/dL



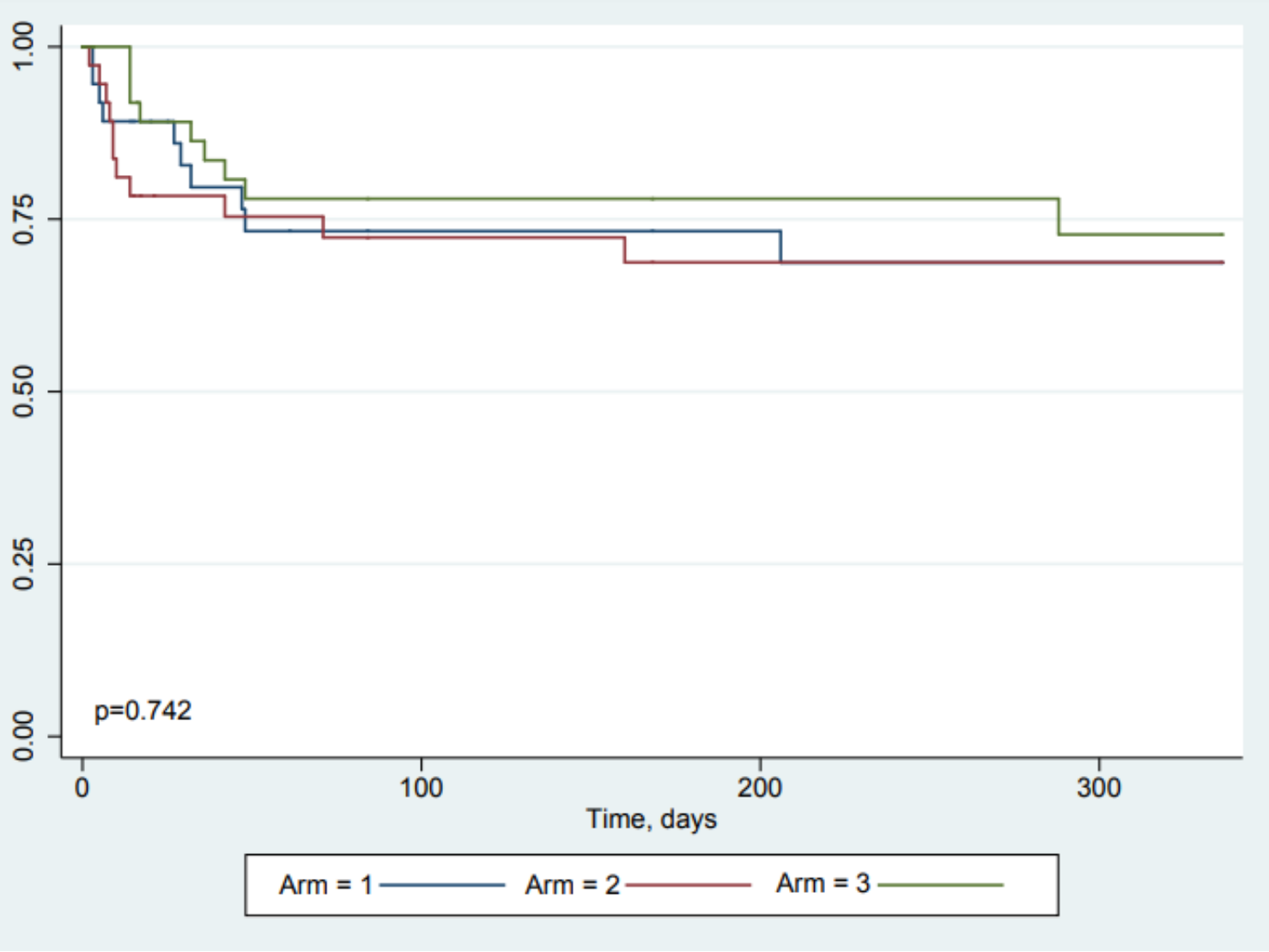
Clinical response Day 14

%

Overall survival



Cumulative probability of survival



Conclusions

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Conclusions

- Single high dose of L-AmB proved to be safe and efficacious as induction therapy of disseminated histoplasmosis in PLWHA.
- No advantage for a second L-AmB dose on day 3.
- Toxicity was not an issue since the interventional arm (10 mg/kg) was as safe as standard therapy.
- A phase III trial is currently being planned.

Thank you for your attention

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@PasqualottoAle

Back up slides

Sample size calculation

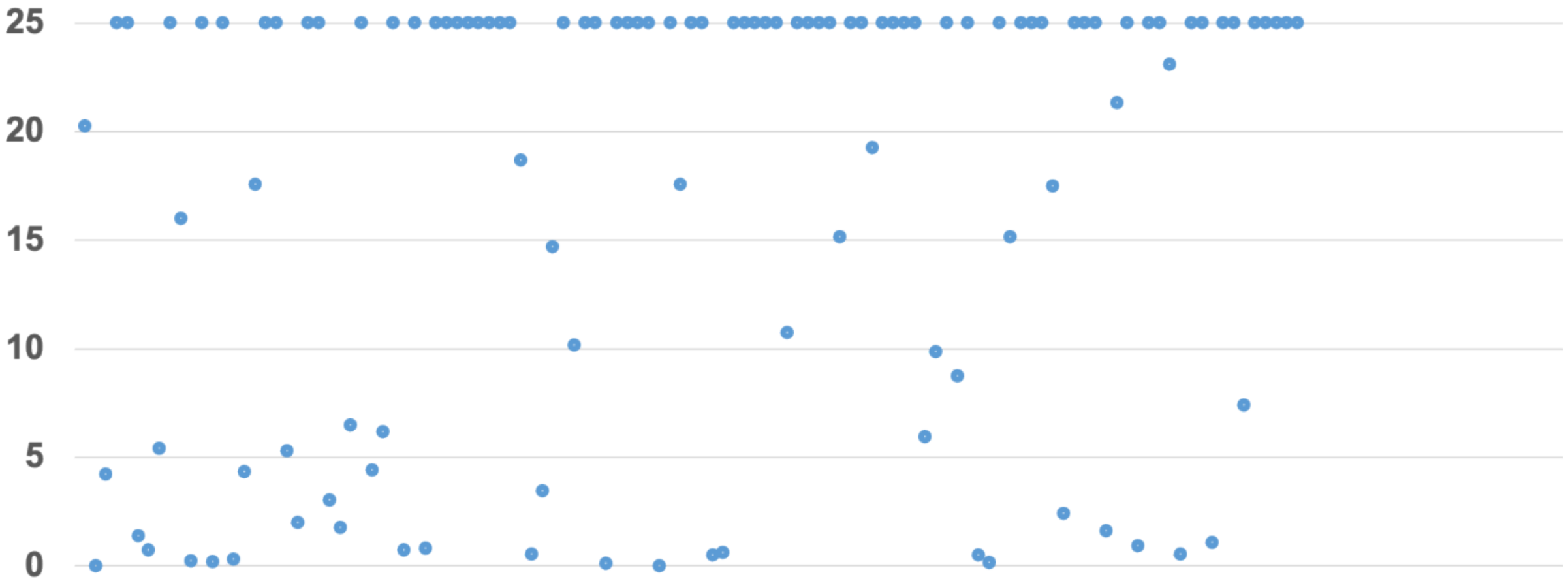
- For each arm, when the sample size is 29, a two-sided 90% CI will extend 10% from the observed proportion for an expected proportion of response equal to 88% [MSG Trial: Johnson PC, *Annals Intern Med* 2002]
- Considering a dropout of 10%, the sample size per arm will be 33, and the total sample size for the study was 99 patients

Determination of liver toxicity

DAIDS Adverse Event Grading Tables

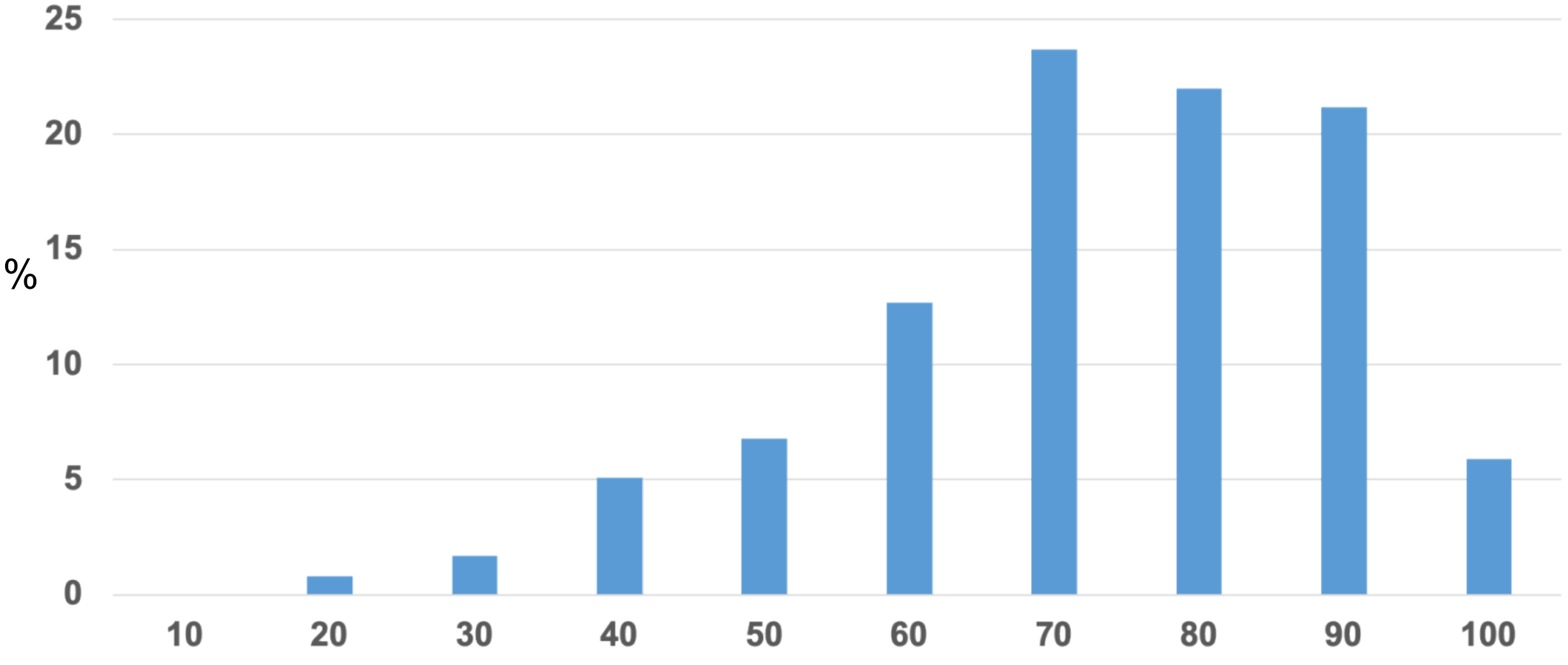
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN

Histo urinary antigen indices - baseline

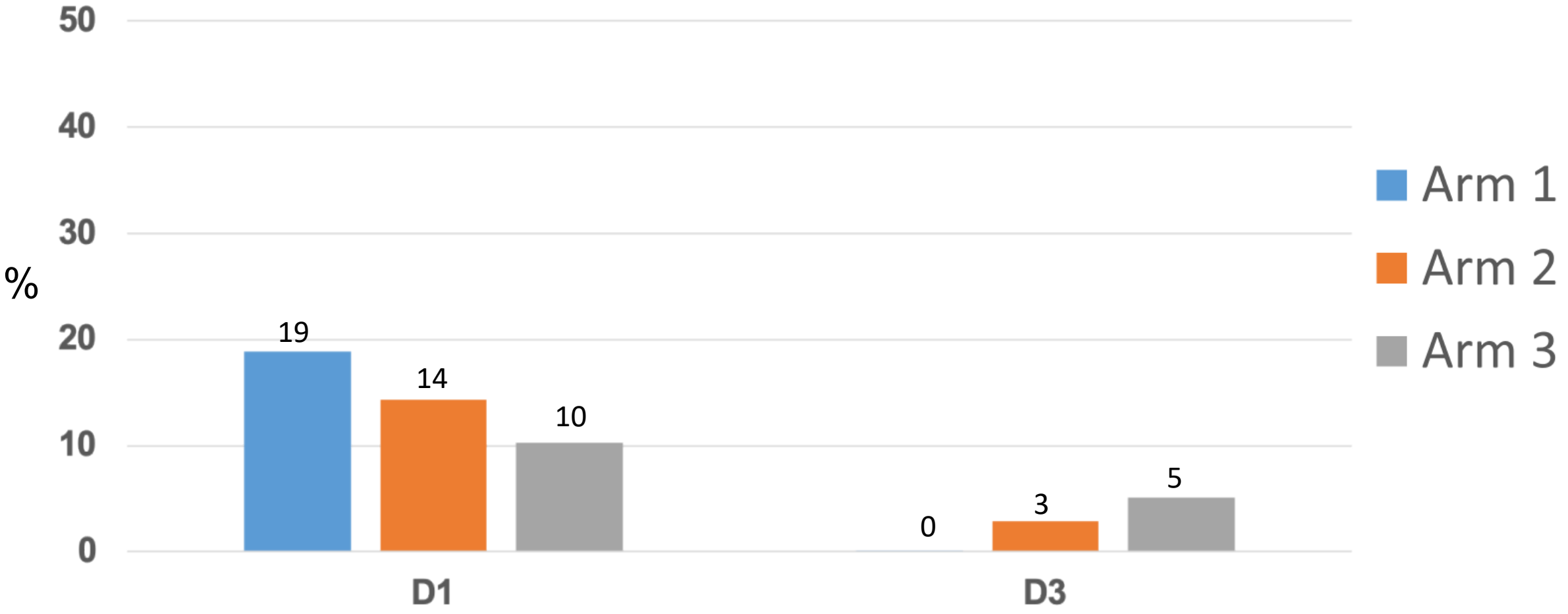


Median 31.23 (range, <0.01-500)

Karnofsky Performance status

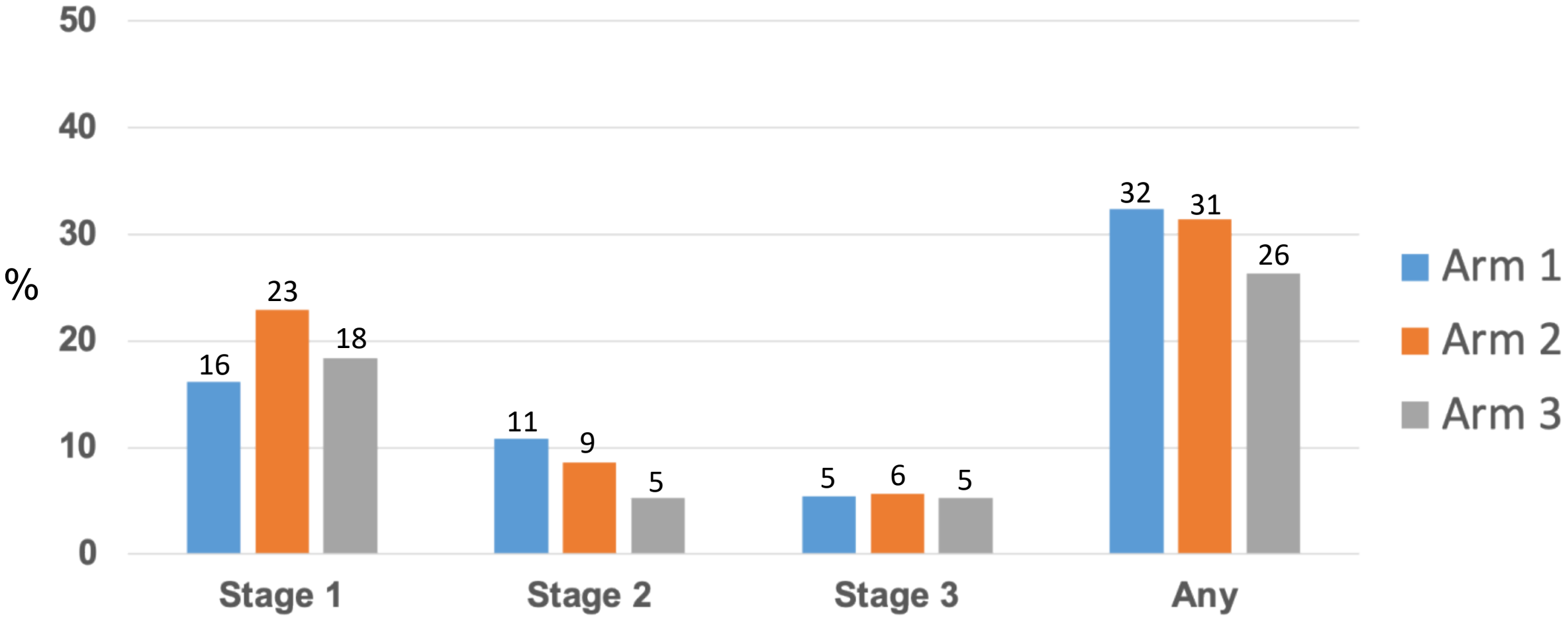


Infusion-related toxicity

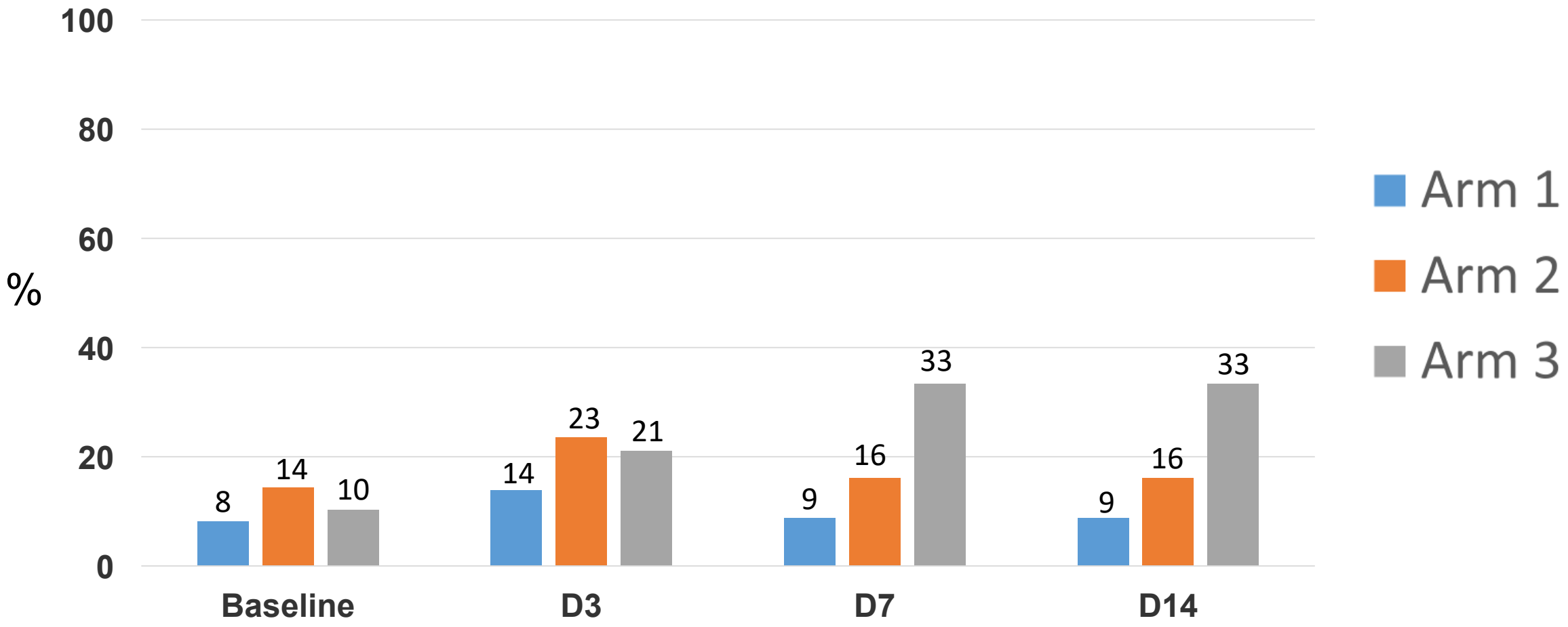


Not resulting in drug withdrawal

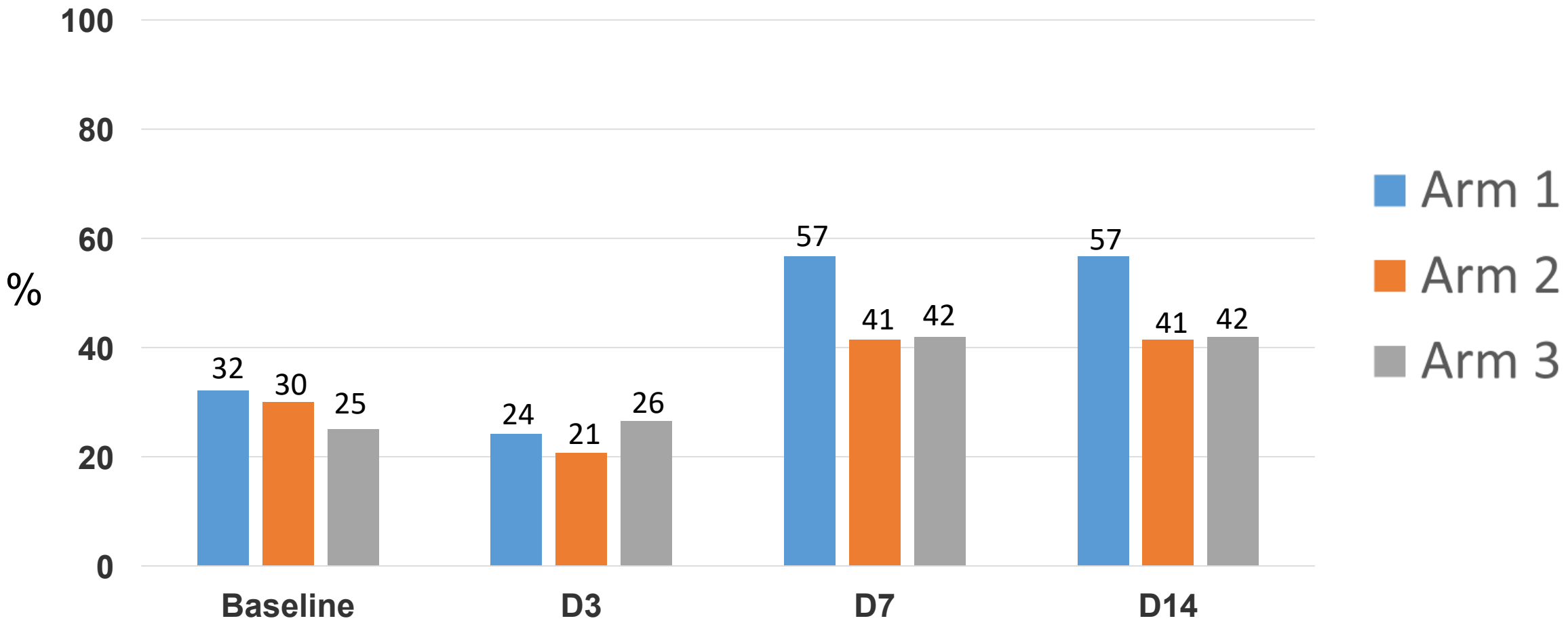
Kidney toxicity Day 3



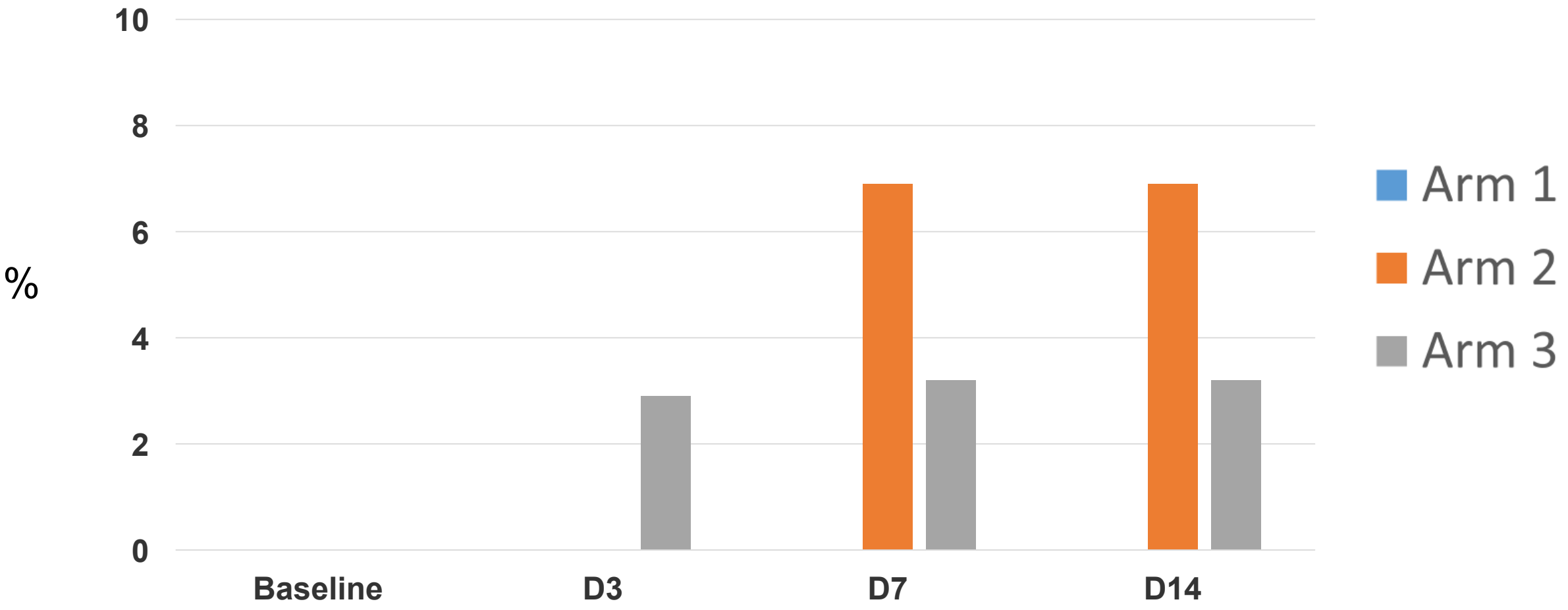
Serum K^+ <3.5 mg/dL



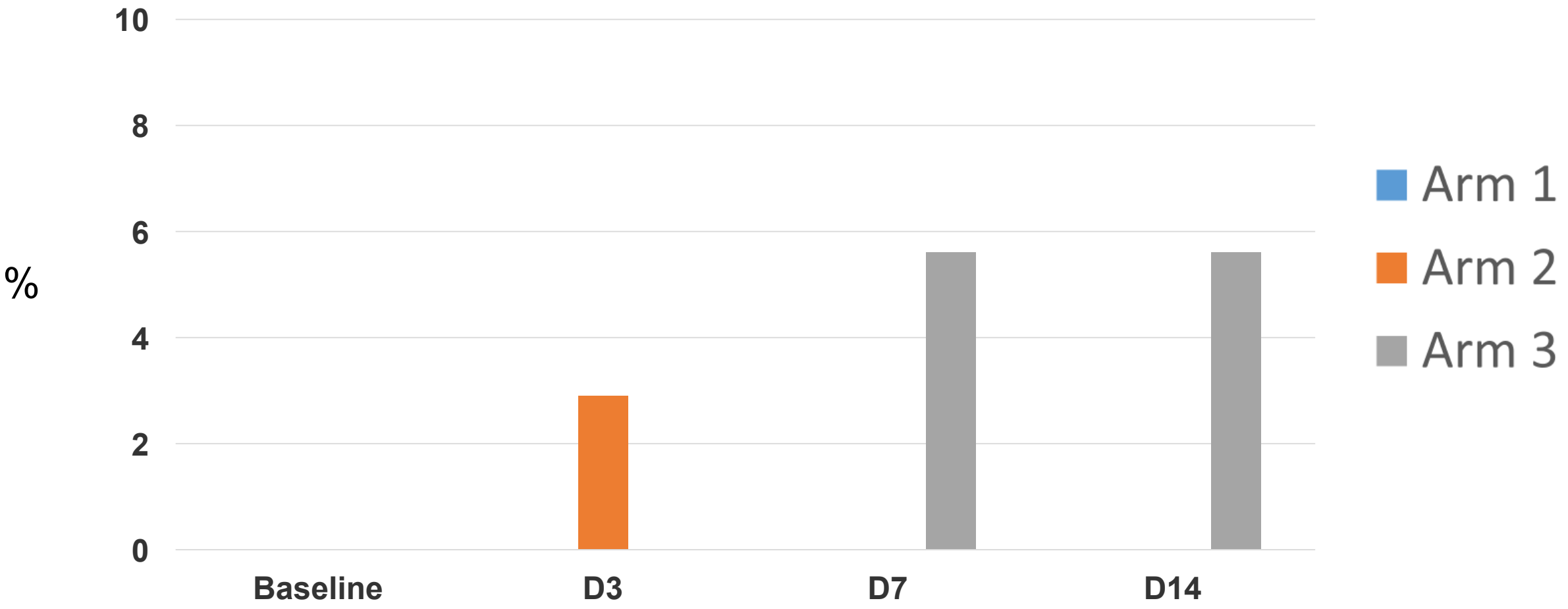
HypoMg^{++} <1.8 mg/dL



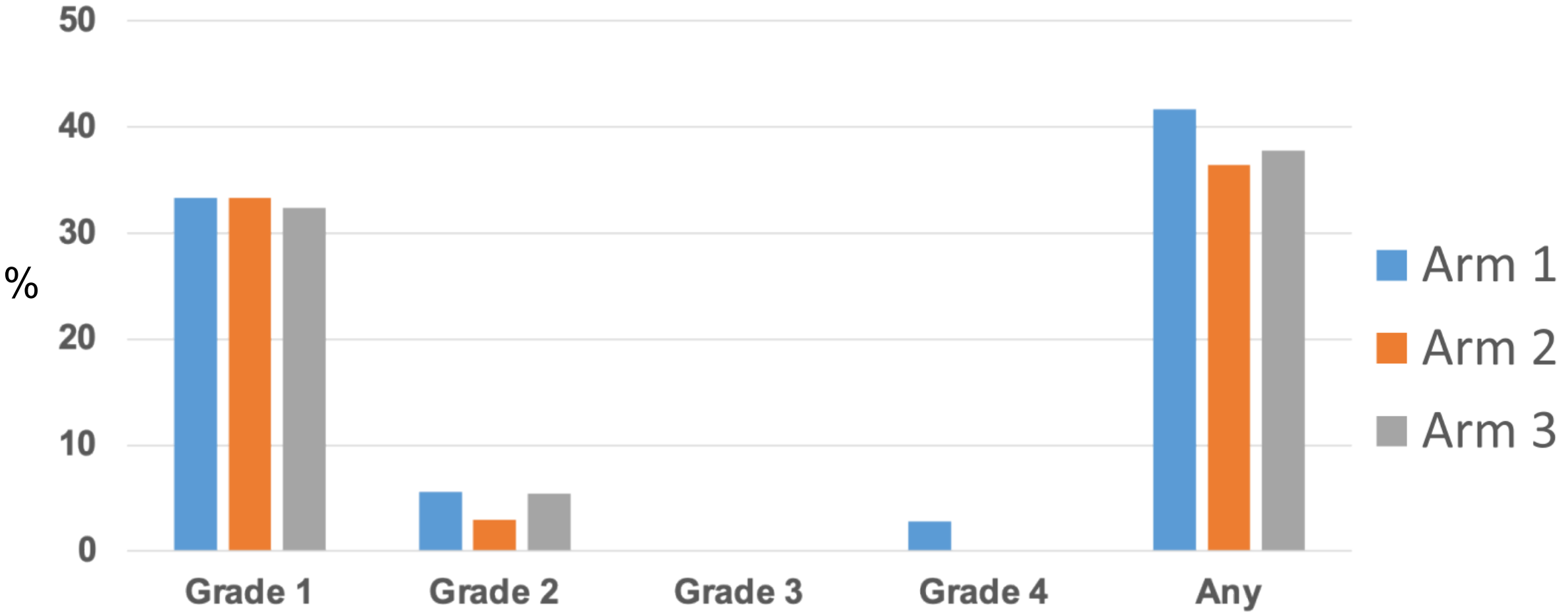
Severe hypoMg^{++} <1.25 mg/dL



Severe hypoK^+ <2.5 mg/dL

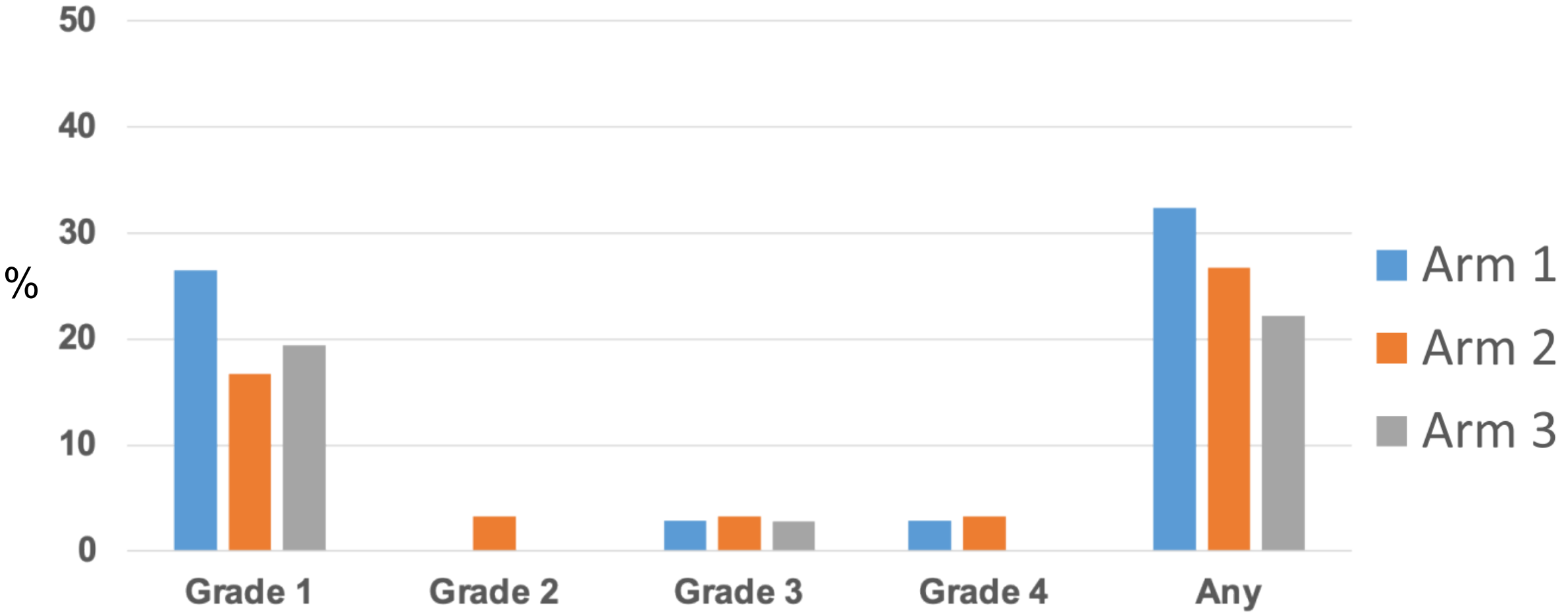


Liver toxicity D3



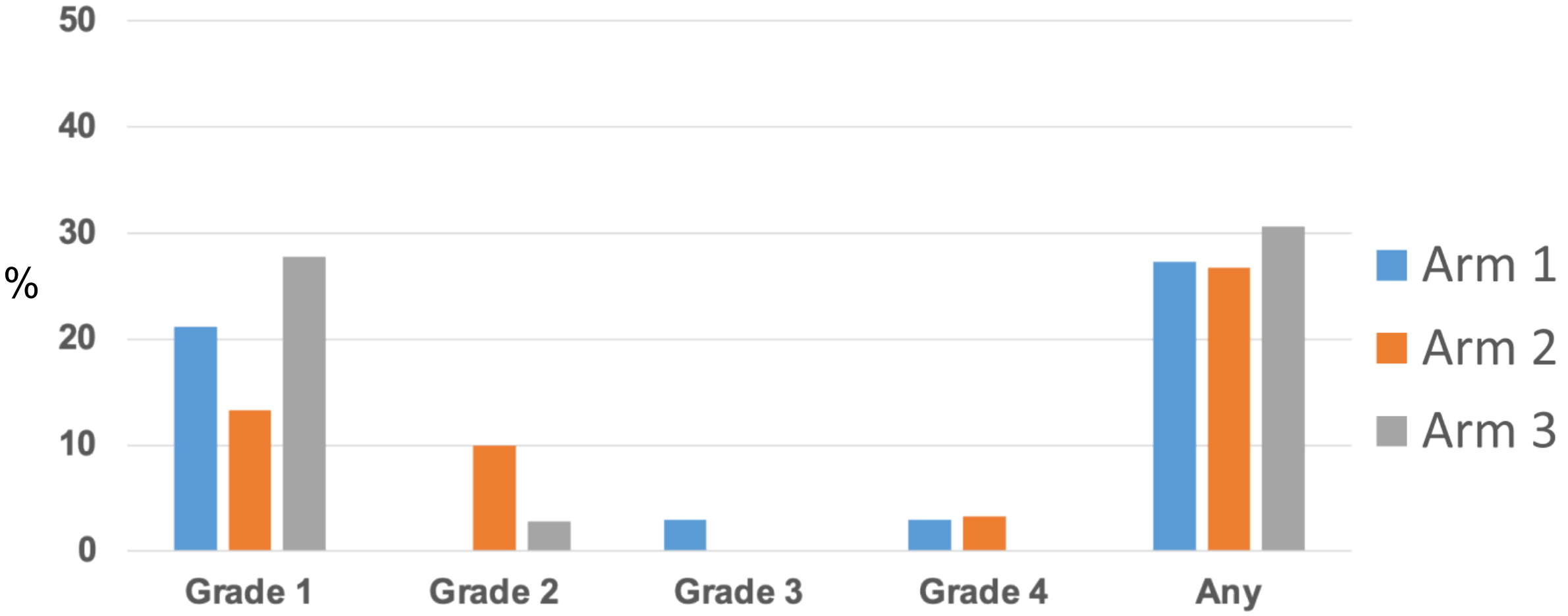
Not resulting in drug withdrawal

Liver toxicity D7



Not resulting in drug withdrawal

Liver toxicity D14

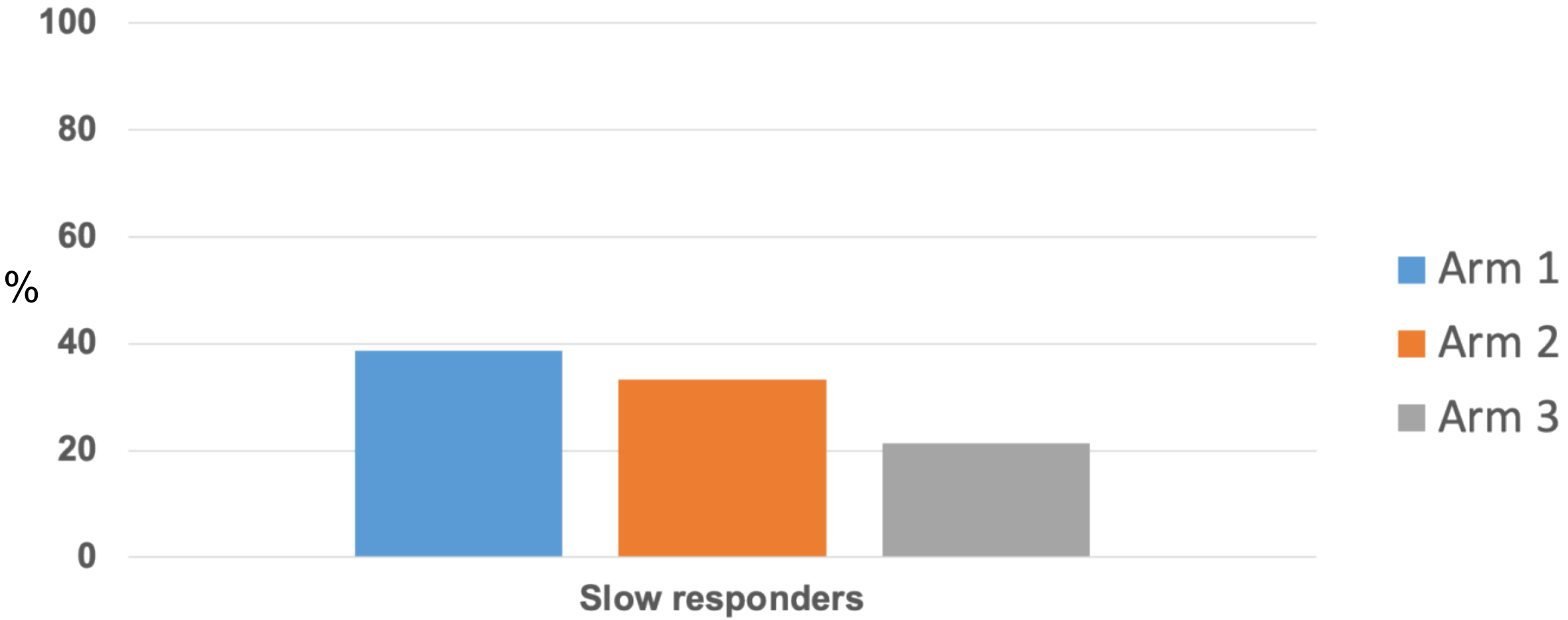


Not resulting in drug withdrawal

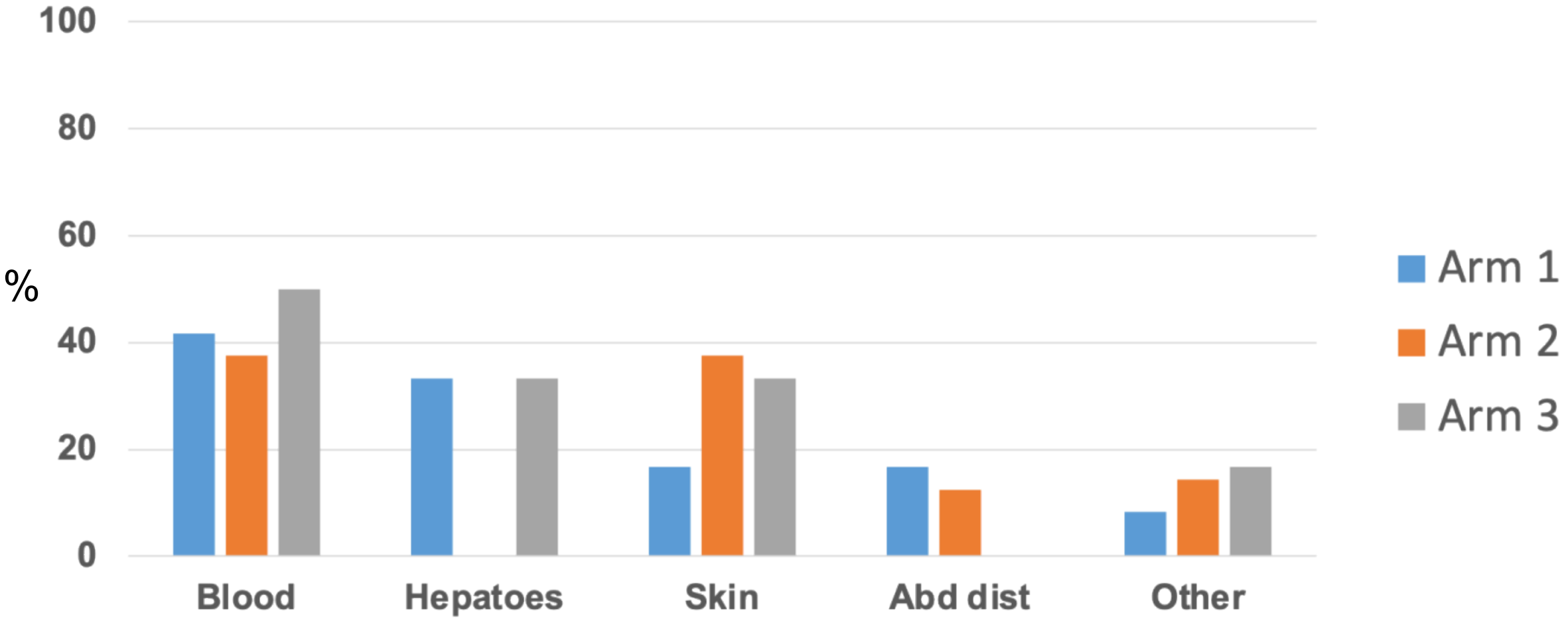
Time for death (median)

- Arm 1: 28 days
- Arm 2: 9 days
- Arm 3: 32 days

‘Slow responders’ (D14)



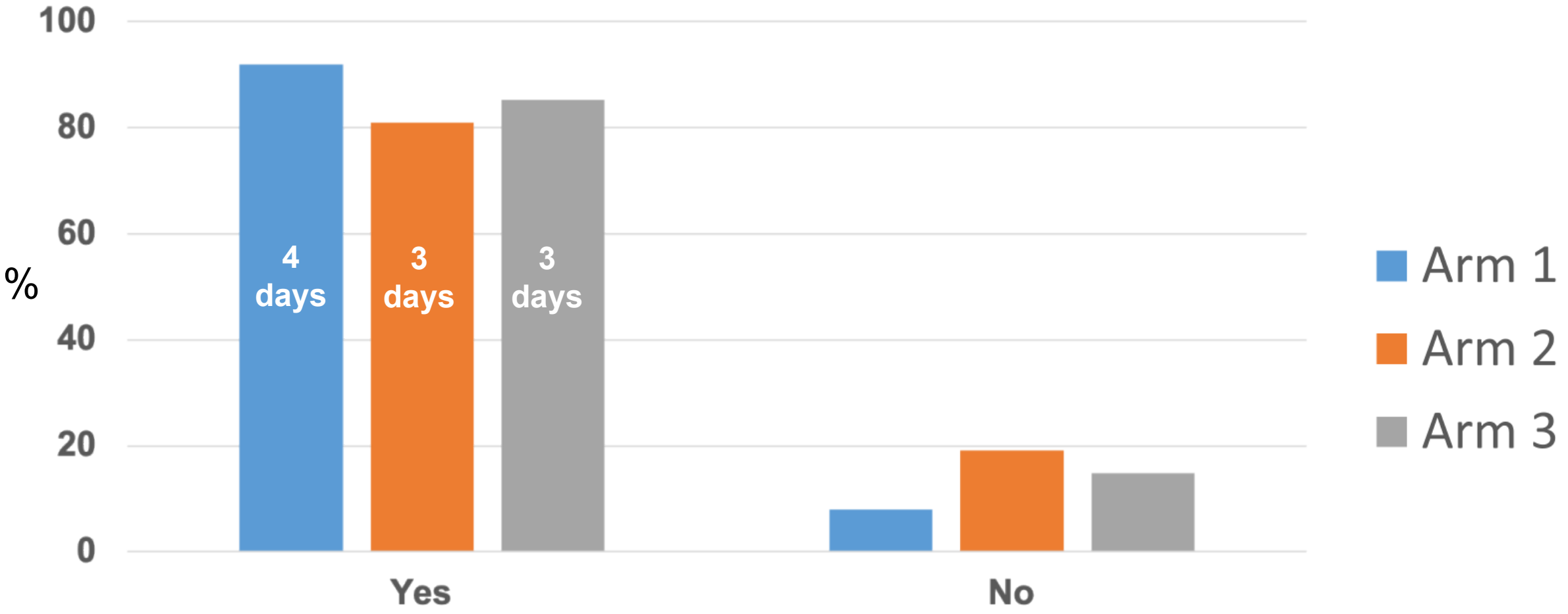
‘Slow responders’ (D14) - reason



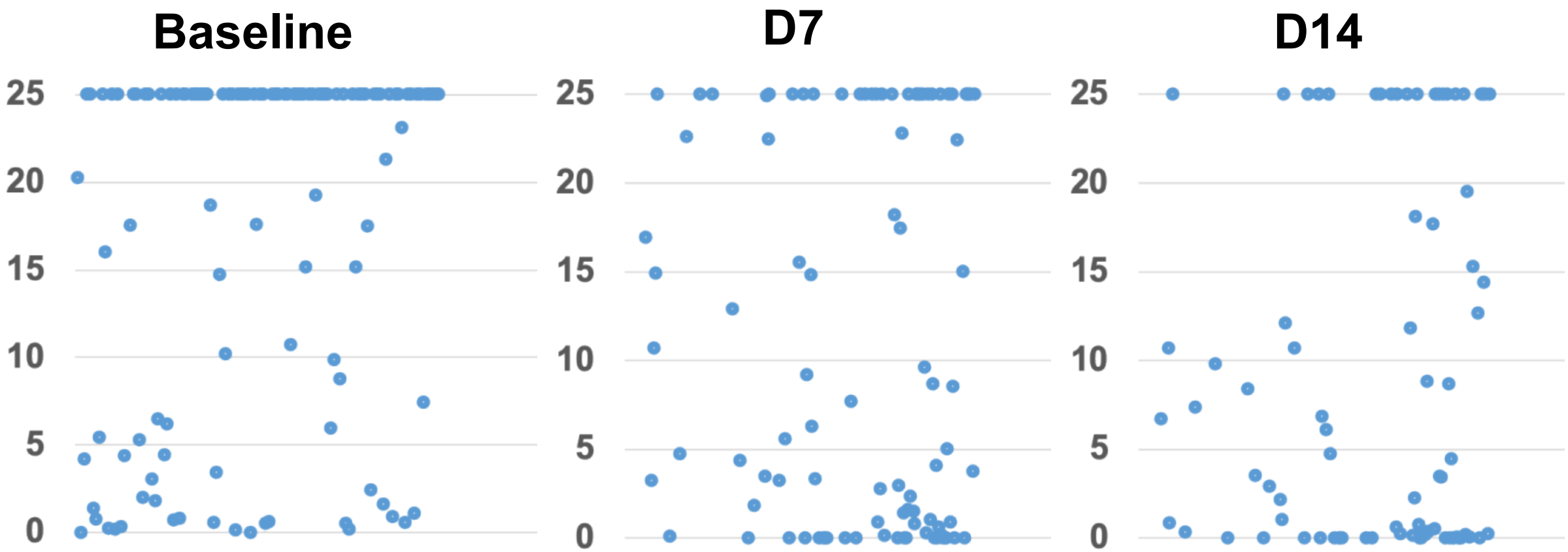
Time for hospital discharge (median)

- Arm 1: 15.0 days
- Arm 2: 14.0 days
- Arm 3: 16.5 days

Afebrile on D14



Histo urinary antigen indices (Immy EIA)

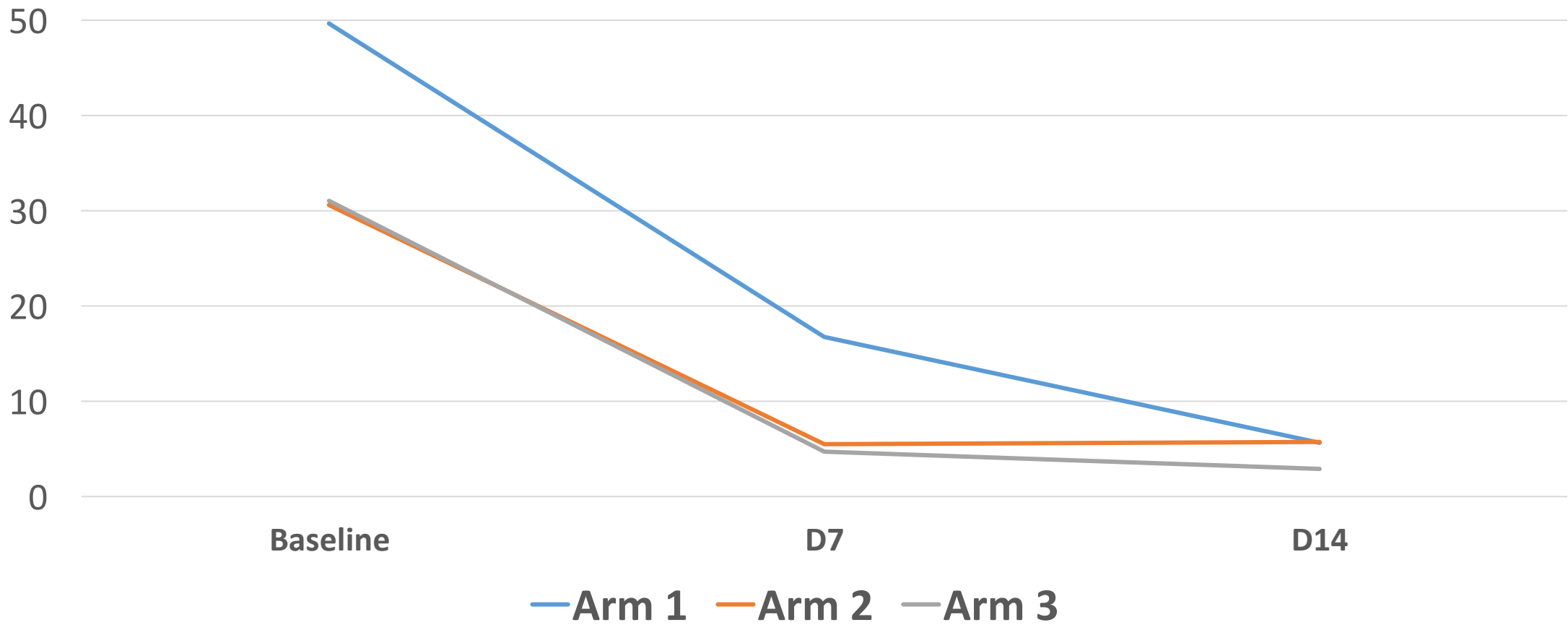


Median 31.23
(range, <0.01-500)

Median 8.60
(range, <0.01-265)

Median 3.96
(range, <0.01-164)

Histo urinary antigen indices per arm



Absence of association between *Histo* antigen titers and outcome

		Baseline	D7	D14
Clinical resolution on D14	Yes	30.9	8.9	4.6
	No	27.1	1.1	0.25