

Can BK virus PCR be a Surrogate Marker in Kidney Transplant Recipients?: A systematic review and meta-analysis

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Background

- Drs. Imlay and Limaye's group provided the new definition for BK nephropathy in kidney transplant recipients (*Imlay et al. CID 2022*)
- BK PCR testing has not been well defined as a **surrogate marker** for BK nephropathy
- Aim: Assess the available global literature to determine whether BK levels in blood or urine correlate with BK nephropathy in kidney transplant recipients

Research questions

- Does BK DNAemia correlate with BK nephropathy?
 - Does high-level BK DNAemia correlate with BK nephropathy?
- Does BK DNAuria correlate with BK nephropathy?
 - Does high-level BK DNAuria correlate with BK nephropathy?
- Does decreasing levels of BK viremia correlate with reducing or preventing BK nephropathy?
- Does decreasing levels of BK viuria correlate with reducing or preventing BK nephropathy?
- Is improvement of BK nephropathy findings (with serial biopsy) correlated with BK viral load reduction (in blood and/or urine)?

in kidney transplant recipients



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Inclusion criteria

- **Population** – Kidney transplant recipients of any age
- **Intervention** – BK DNAemia or DNAuria after transplantation
- **Comparison** – No BK DNAemia or DNAuria after transplantation
- **Outcomes** BKVAN as defined by the study and BKVAN proven by biopsy
- **Timing** – Any time from transplant to outcomes evaluation
- **Study design** – Observational clinical studies, randomized controlled trials, case series if >10 cases; conference proceedings if data was sufficient

Additionally, studies on **follow-up biopsies** after BKVAN diagnosis with serial BK VL measurements – to assess for improvement of BKVAN findings with BK VL reduction



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Exclusion criteria



Poster/conference abstract/letters with insufficient data, case report/study, reviews, editorials, opinion articles without original data



Animal studies



No measurement of quantitative polymerase chain reaction (PCR) eg. antigenemia, mRNA, qualitative PCR



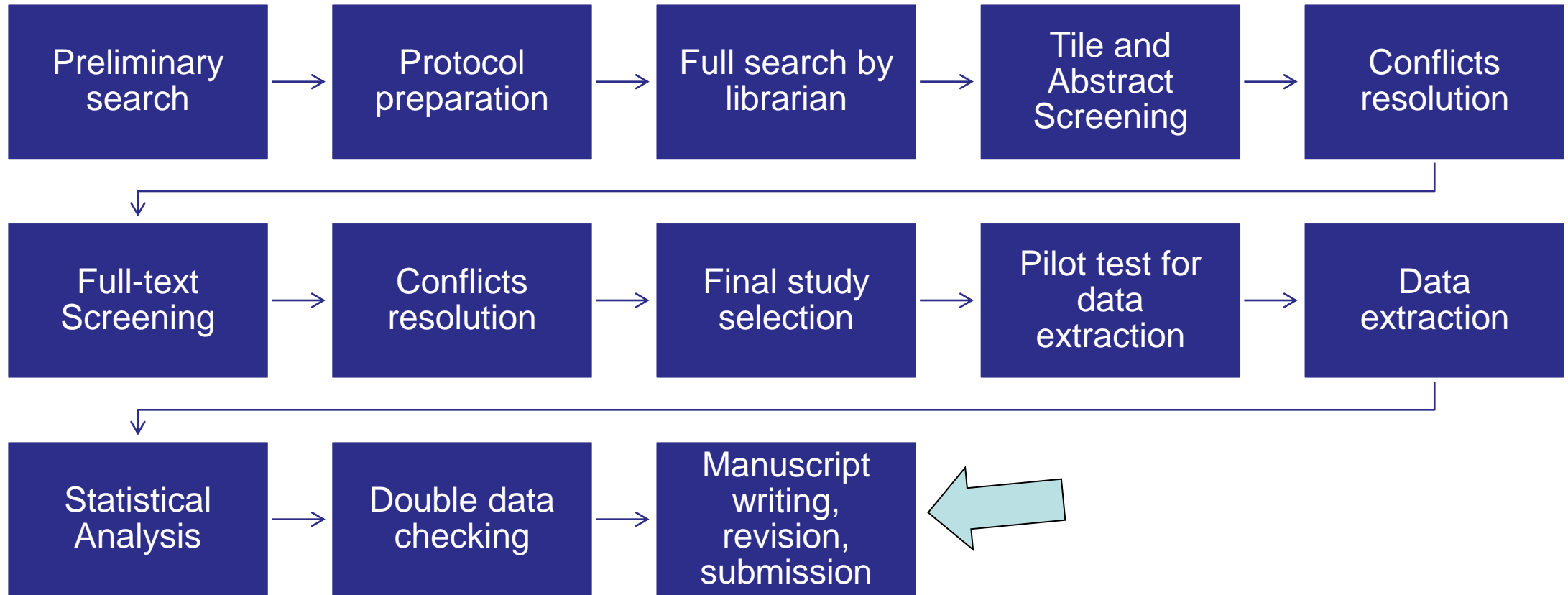
Only laboratory data without clinical information

Search methods

- Search engines: Medline, Embase, Scopus, Web of Science, CINAHL Plus with Full Text
- Software: COVIDENCE
- Search terms:
 - Kidney
 - Transplant(s), Graft, Allograft(s), Allotransplant, Autograft, Transplant recipients; Organ transplantation; Transplantation, autologous; Transplantation, heterotopic; Transplantation, homologous
 - BK virus, BKV, BKPyV, polyomavirus, polyomavirus infections
 - Viremia, viraemia, viral load, virus load, viral burden, virus burden, virus titer, virus titre, viral titer, viral threshold, DNAemia, Viruria, viruria
- Preliminary search: August 2019
- Updated search: January 2023



Steps



RESULTS



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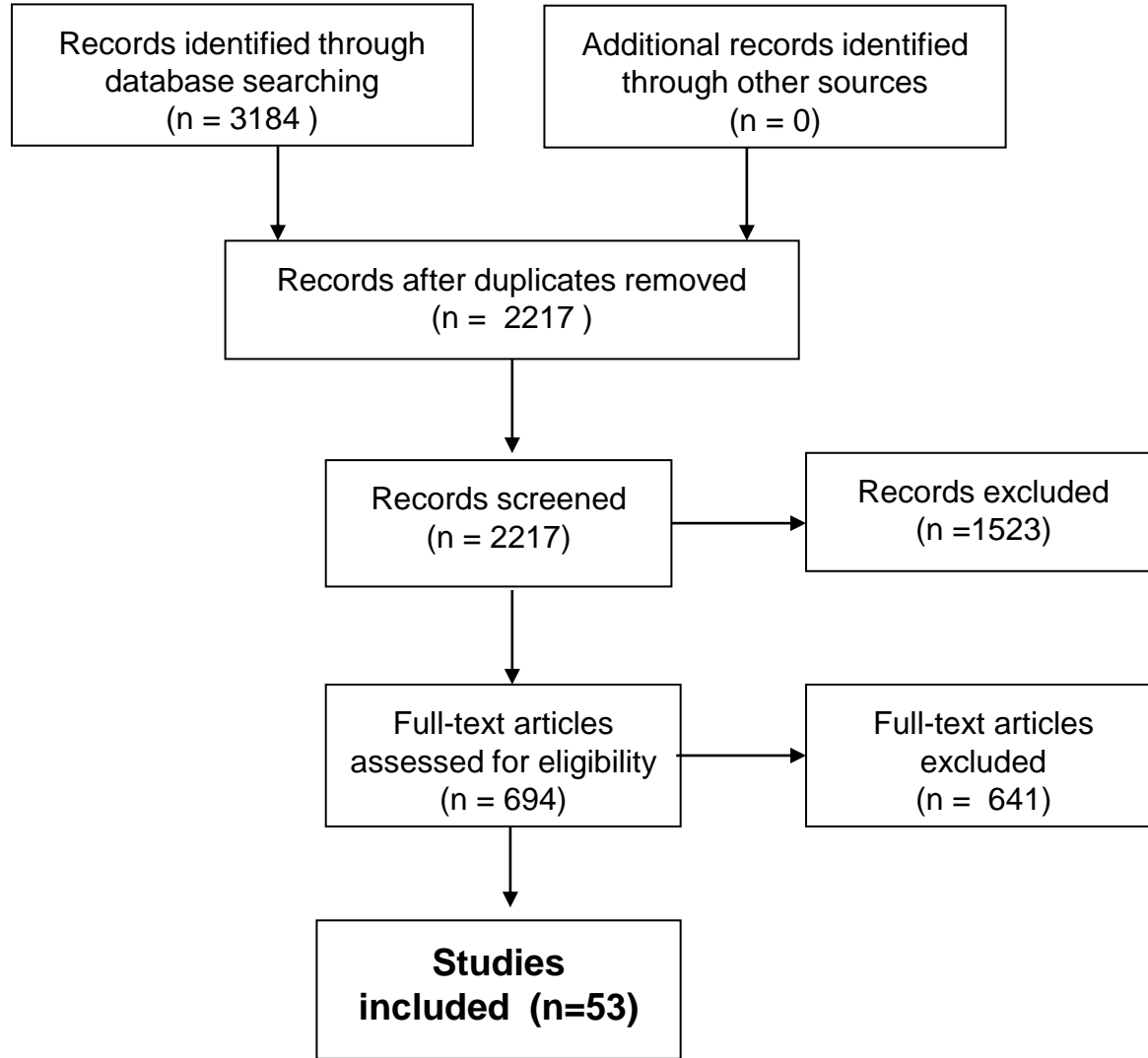
PRISMA diagram

Identification

Screening

Eligibility

Included

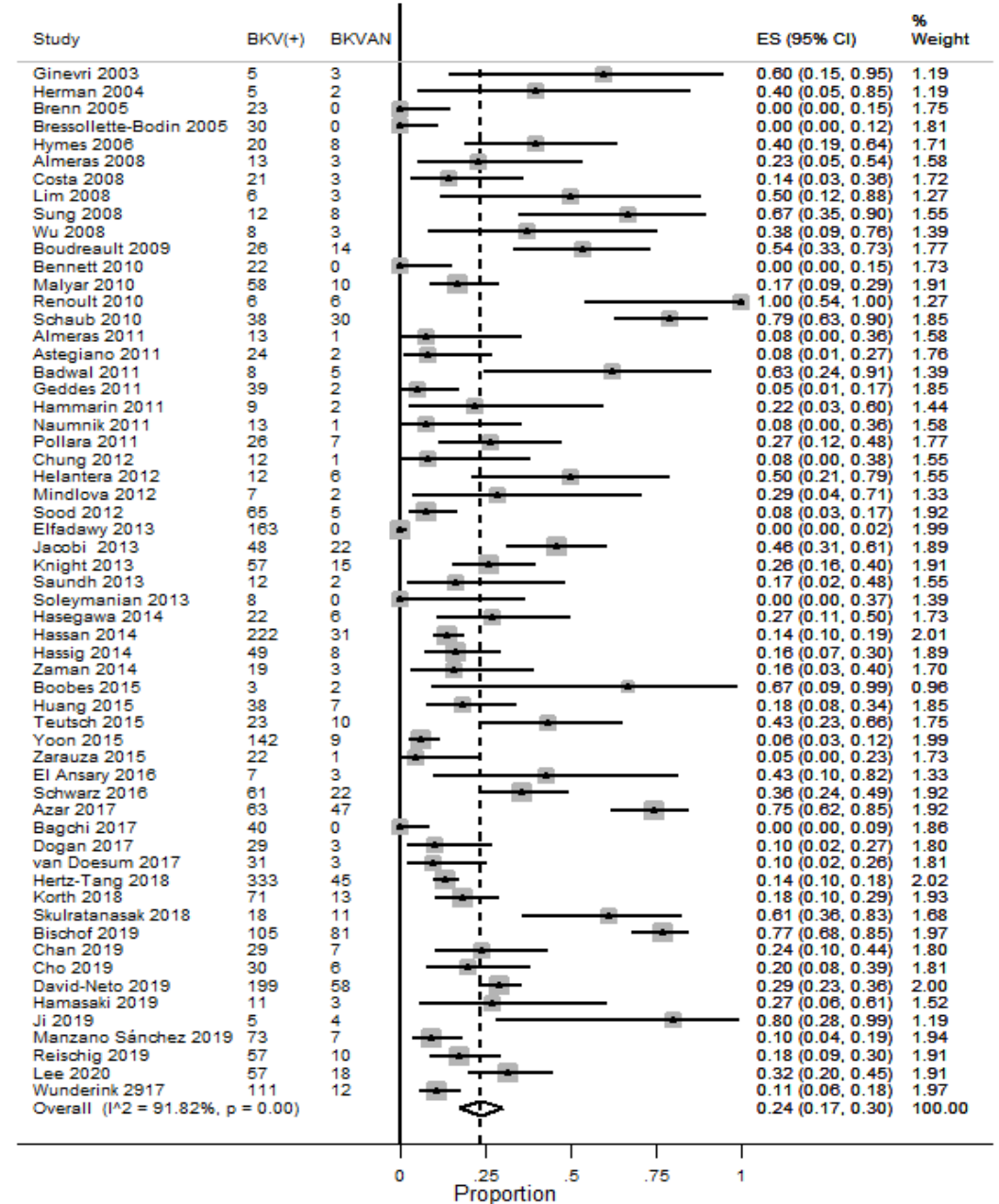


Does BK viremia correlate with BKVAN (any definition)?

24% (95% CI 0.17 – 0.30)



BKVAN (any definition) prevalence among those with BK viremia

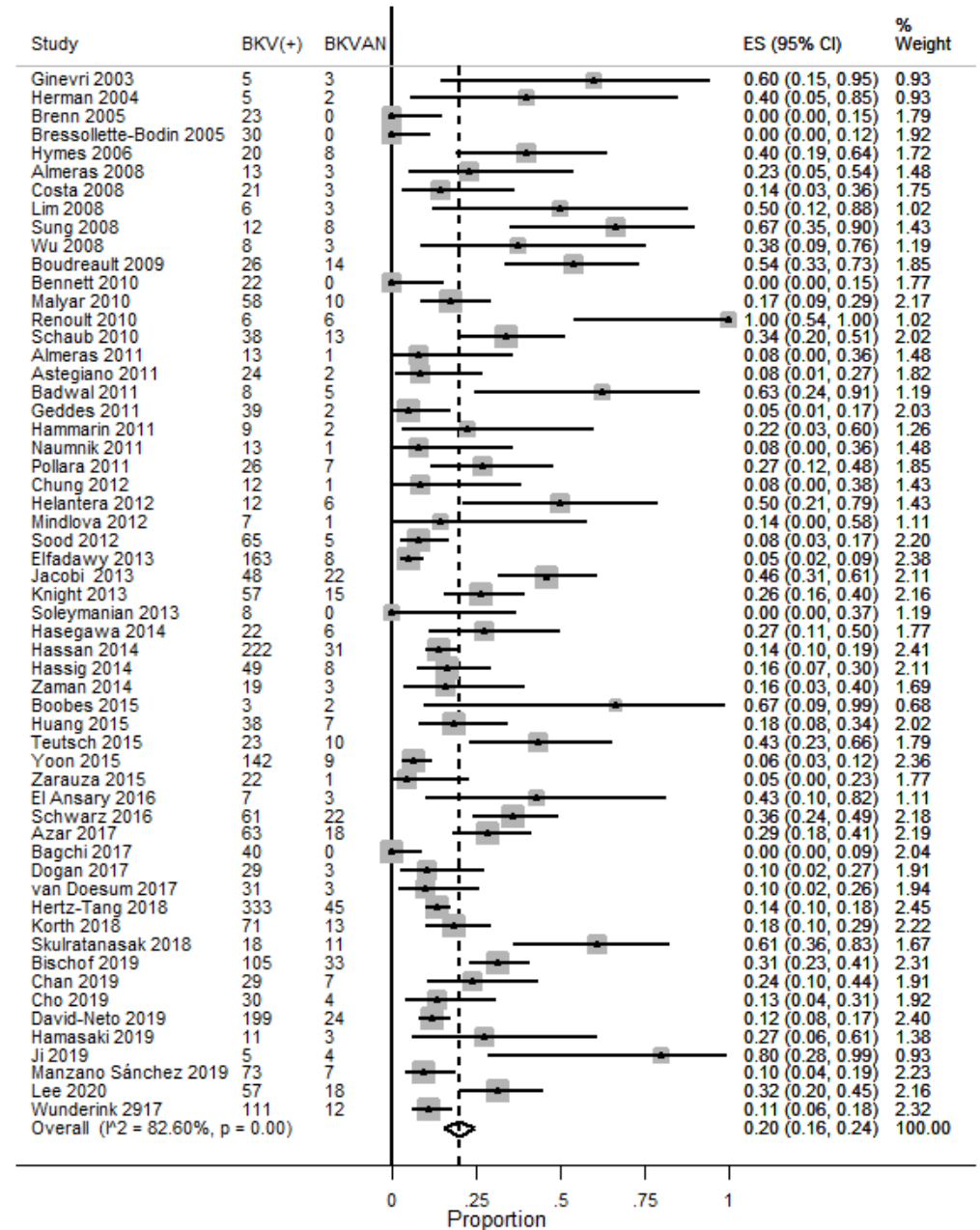


Does BK viremia correlate with biopsy-proven BKVAN?

20% (95% CI 0.16 – 0.24)



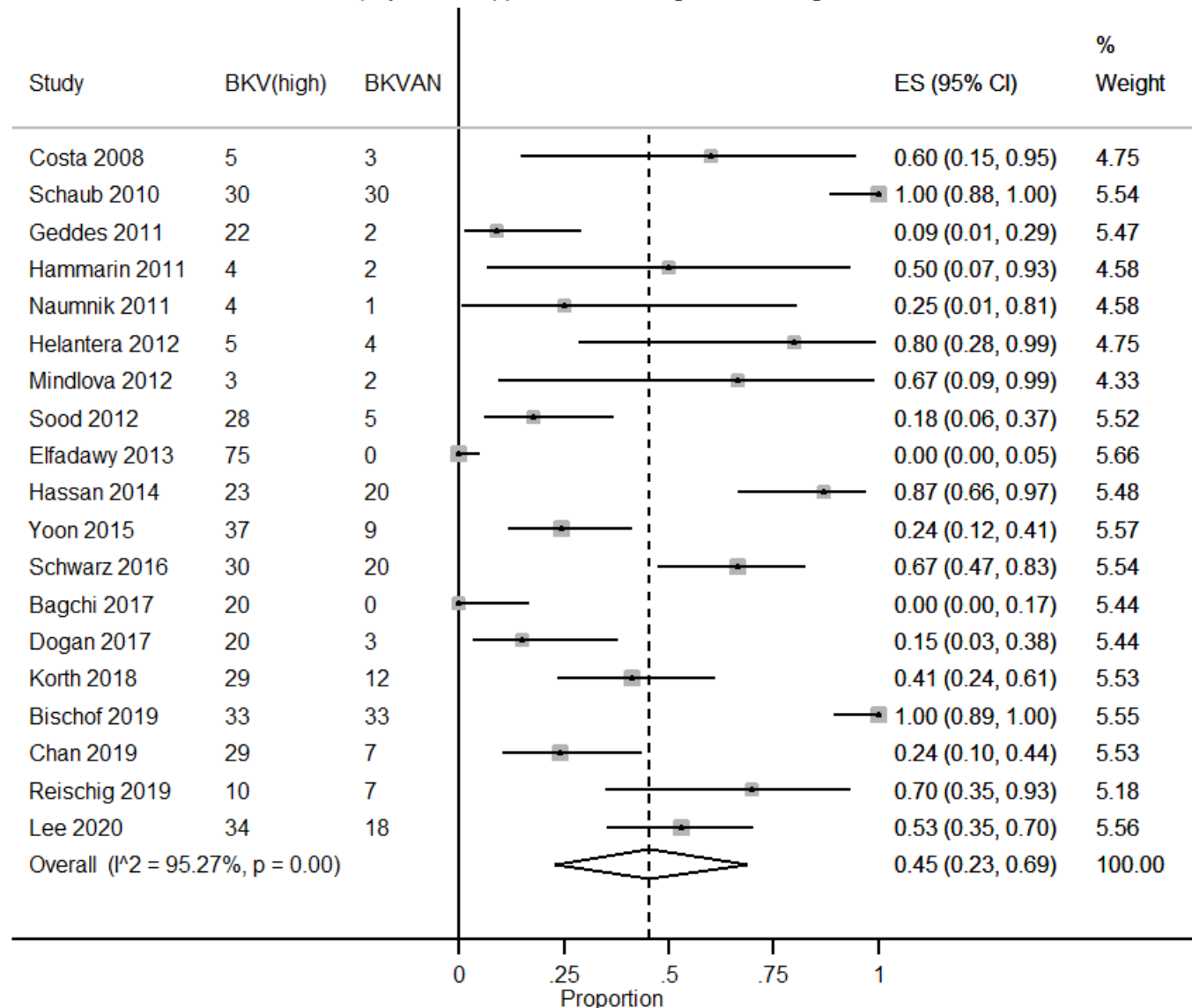
BKVAN (biopsy-confirmed) prevalence among those with BK viremia



Does high-level BK viremia correlate with BKVAN (any definition)?

45% (95% CI 0.23 – 0.69)

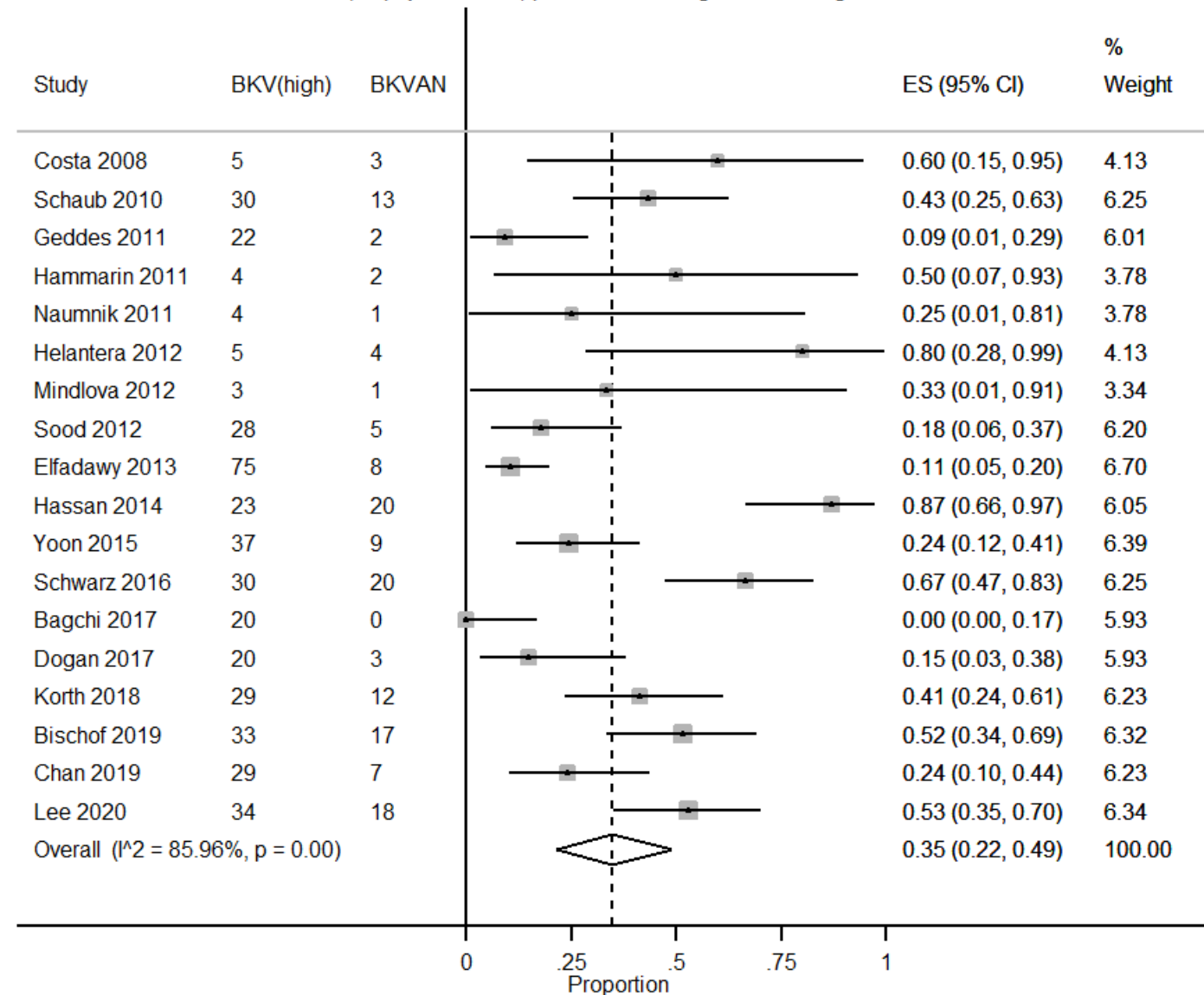
BKVAN (any definition) prevalence among those with high BK viremia



Does high-level BK viremia correlate with biopsy-proven BKVAN?

35% (95% CI 0.22 – 0.49)

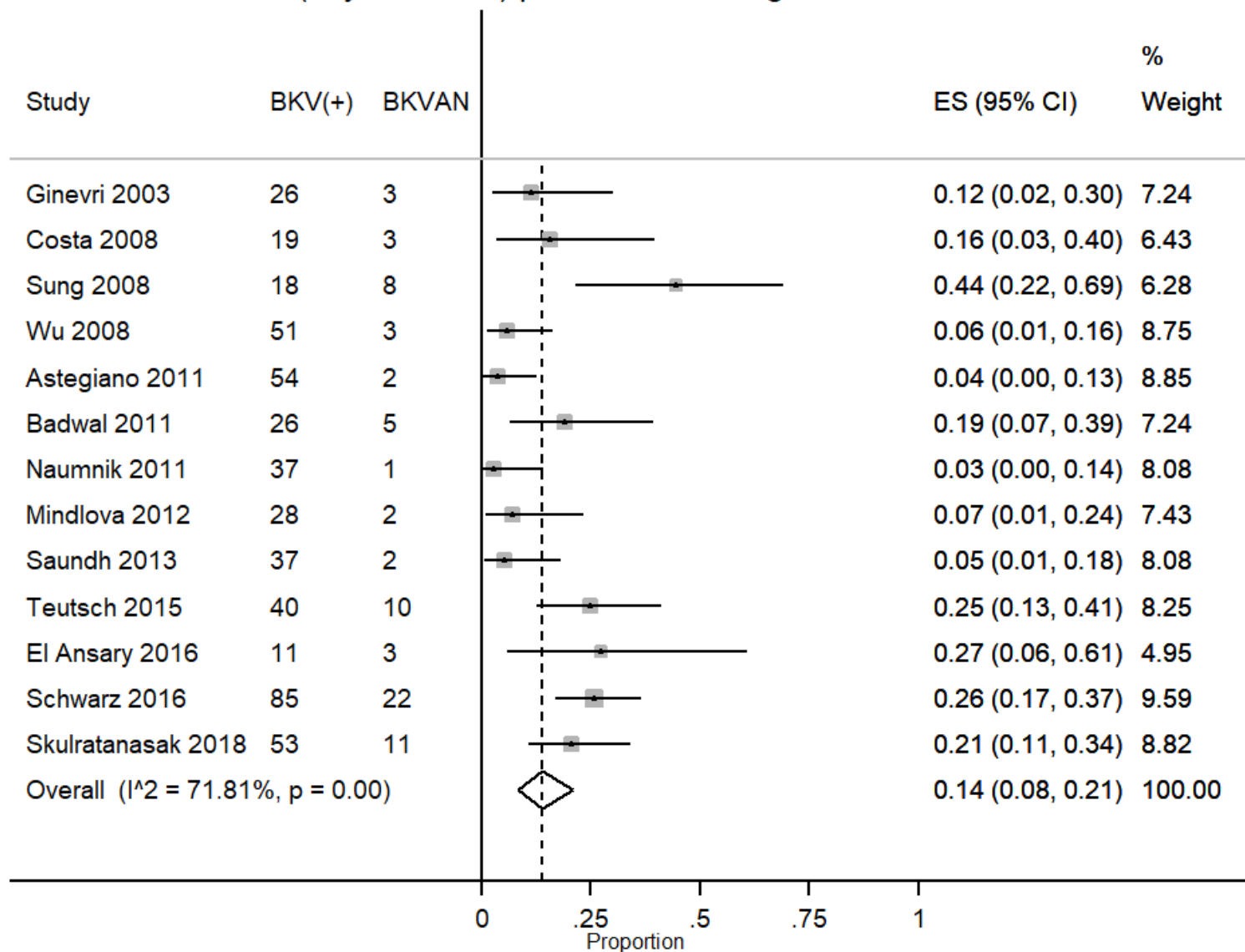
BKVAN (biopsy-confirmed) prevalence among those with high BK viremia



Does BK DNAuria correlate with BKVAN (any definition)?

14%
(95% CI 0.08 – 0.21)

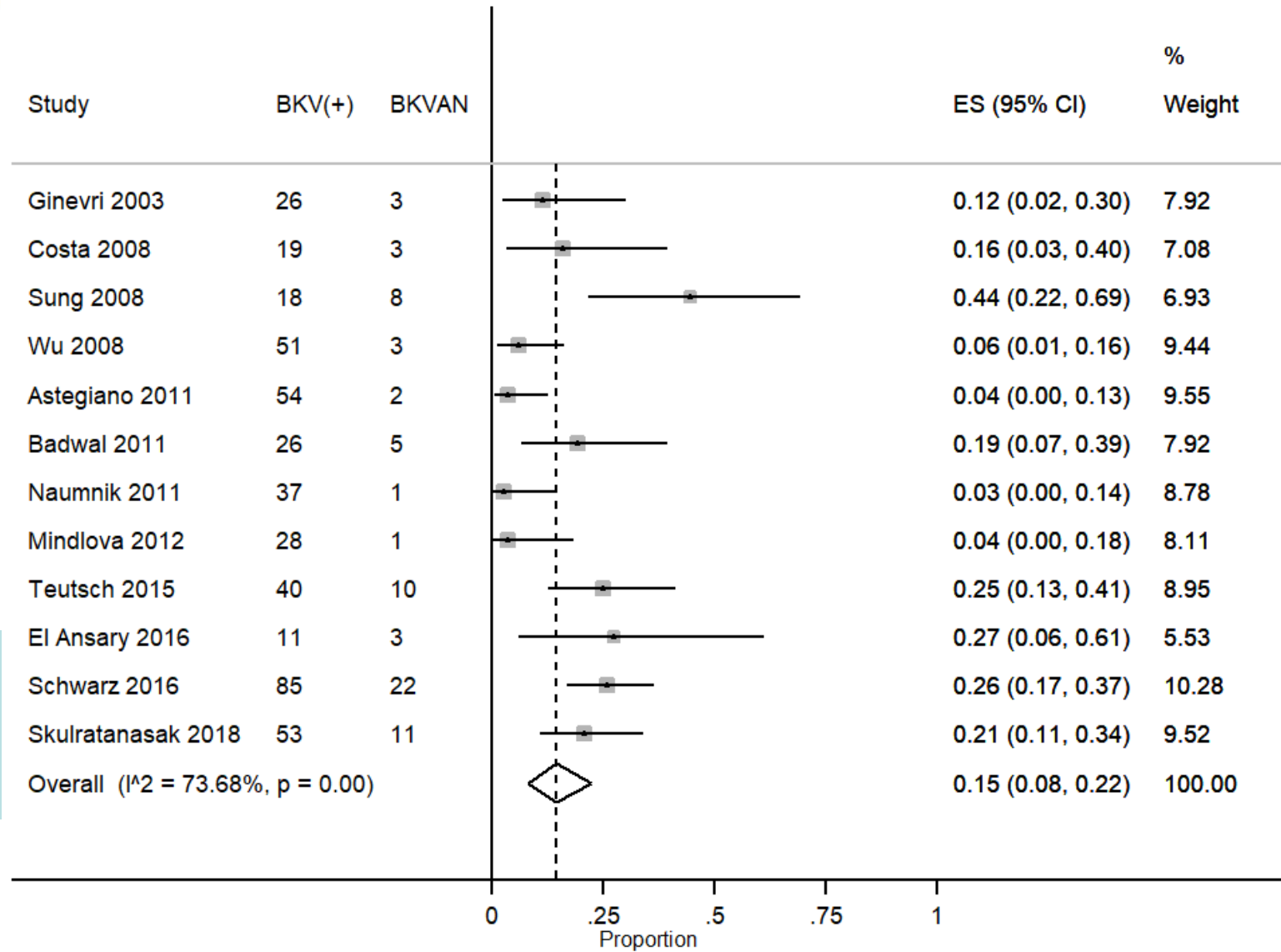
BKVAN (any definition) prevalence among those with BK viruria



Does BK DNAuria correlate with biopsy-proven BKVAN?

15%
(95% CI 0.08 – 0.22)

BKVAN (biopsy-confirmed) prevalence among those with BK viruria

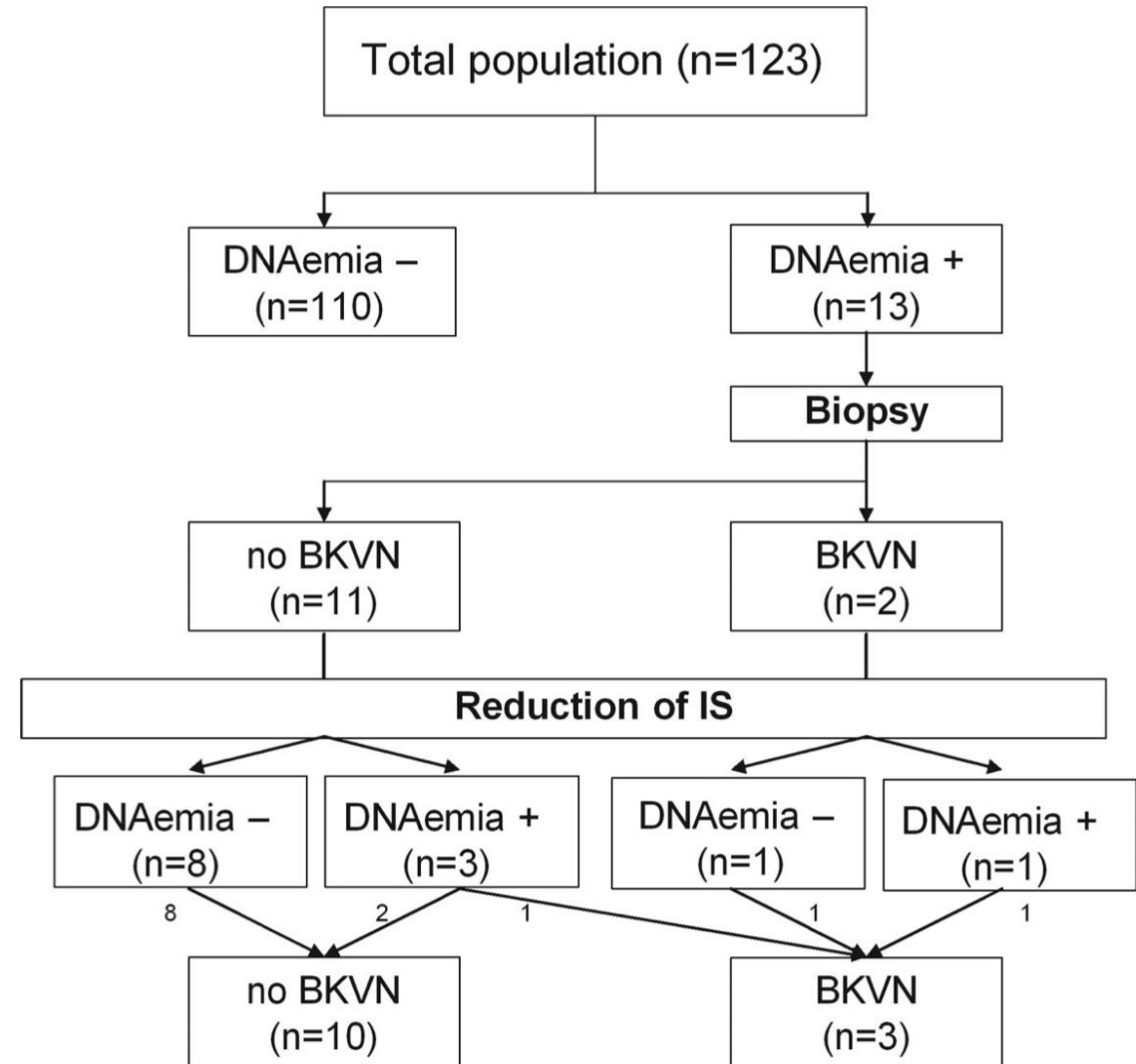


Does decreasing levels of BK DNAemia correlate with reducing or preventing BKVAN?

- Several studies documented the correlation between BKV DNAemia clearance and BKVAN prevention (Almeras 2007, Bennet 2010, Elfadawy 2014, Brennan 2005, Chung 2012)
- Some studies also showed prolonged/persistent BK DNAemia was associated with BKVAN (Bagchi 2017, Chan 2019, Elfadawy 2014, Huang 2015, Jacobi 2013, Reischig 2019)

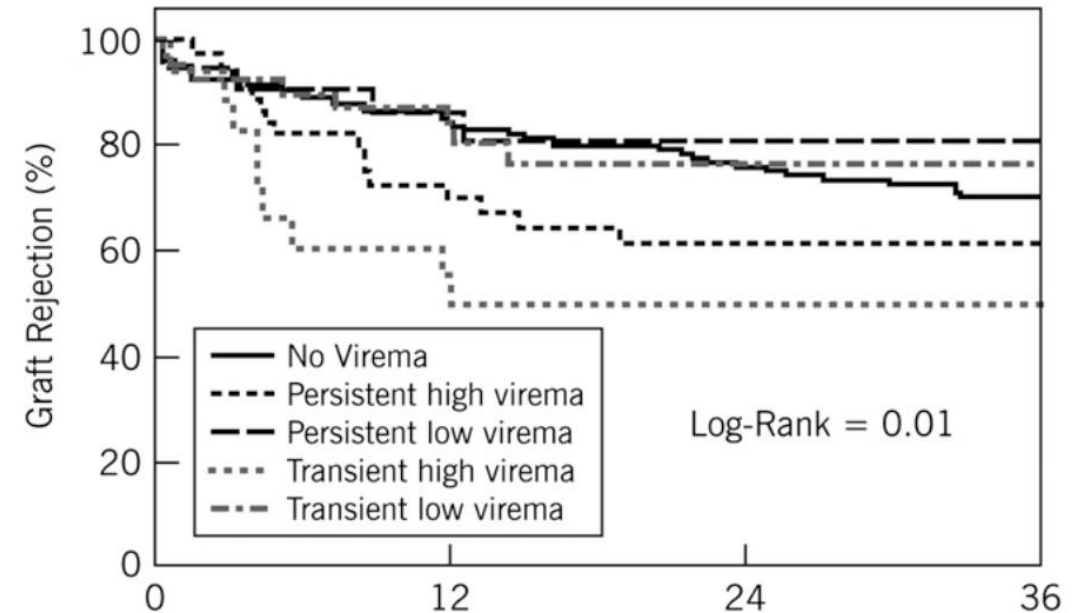
Almeras et al. (Clinical Transplantation 2007)

- Patients without BKVAN on initial biopsy (11): after reduction of IS in patients without BKVN, viremia disappeared in 8 of 11, decreased in 2 of 11, and increased in 1 patient who eventually developed BKVAN
- Patients with BKVAN (2): viremia remained positive in 1 patient and disappeared in the second, but renal function deteriorated in both



Elfadawy (CJASN 2014)

- The incidence of BKVAN was limited to the persistent high viremia group (1.3%, $P < 0.001$).
- Significant difference in graft rejection rates: 21.5% in non-viremia, 17.3% in persistent low viremia, 19% in transient low viremia, 34% in persistent high viremia, and 50% in transient high viremia.



	Patients at Risk			
	0	12	24	36
No Viremia	479	311	193	75
Persistent high viremia	47	29	19	11
Persistent low viremia	23	17	7	2
Transient high viremia	18	11	4	1
Transient low viremia	42	28	10	4

Does decreasing levels of BK DNAuria correlate with reducing or preventing BKVAN?

- Boobes 2015: 17 patients with DNAuria treated by reduction of immunosuppression, all of them cleared DNAuria. None of them developed BKVAN.
- Bennet 2010: 34 patients with DNAuria. No BKVAN was observed after reducing mycophenolate (surveillance biopsies)

Is improvement of BK nephropathy findings (with serial biopsy) correlated with BK viral load reduction (in blood and/or urine)?



8 studies



Persistent high BKV DNAemia correlated with increased risk of graft loss



Correlation between viral load clearance and improvement of pathology findings in serial biopsies

Omic (Frontiers in Medicine 2021)

- Follow-up period of 24 months after biopsy
- Multivariable regression model: absolute viral load change was a significant risk factor for graft survival - each log unit drop in absolute viral load decreased the risk for graft loss by 22%.

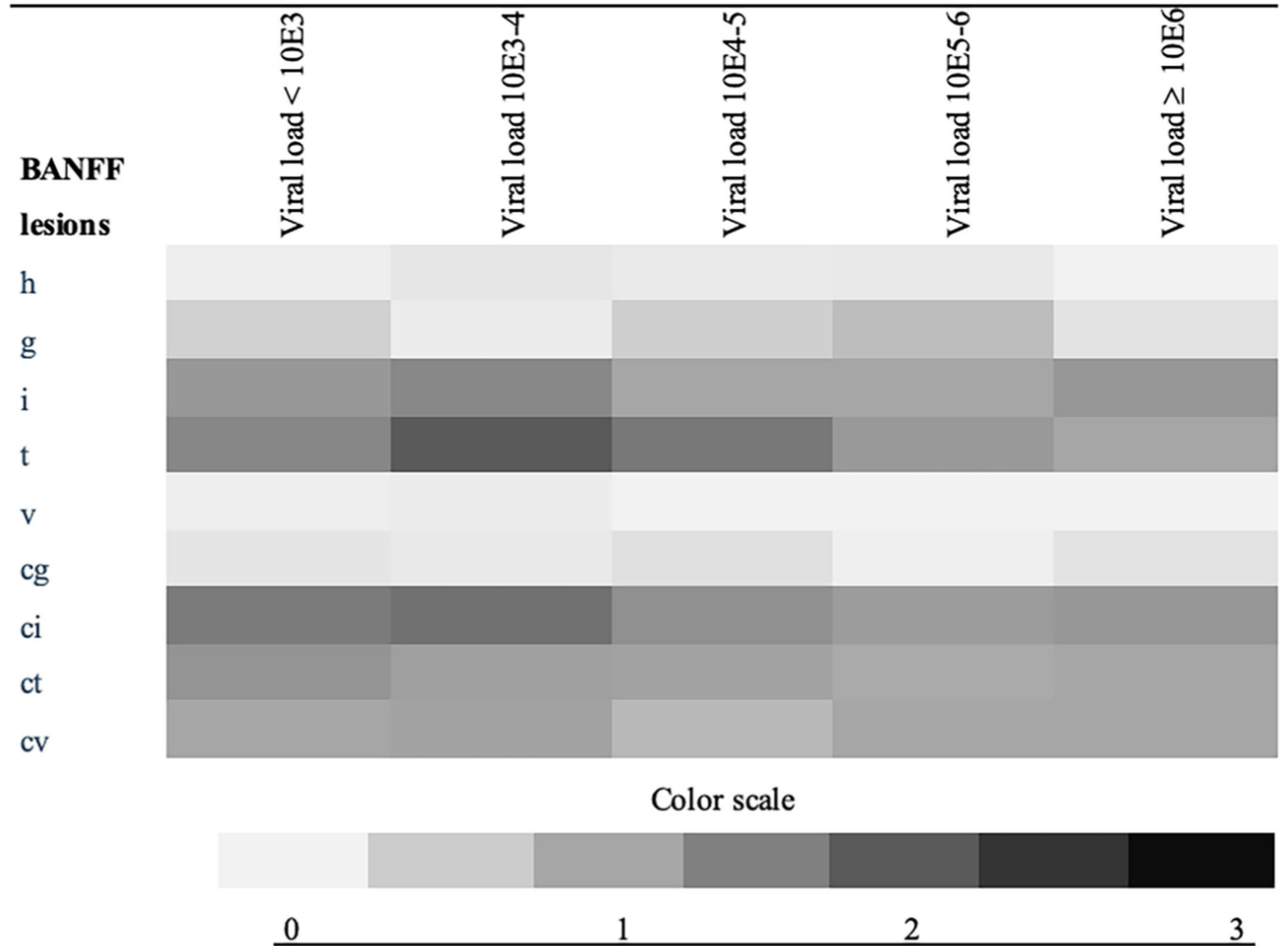


FIGURE 4 | Heat map of BANFF single lesions in the index biopsy in relation to absolute viral load; shows the mean value of BANFF scores (color scaled) at the index biopsy according to the viral load at the time of the diagnosis, (copies/ml), h, arteriolar hyalinosis; g, glomerulitis; i, interstitial inflammation; v, intimal arteritis; t, tubulitis; cg, transplant glomerulopathy; ci, interstitial fibrosis; ct, tubular atrophy; cv, arterial fibrous intimal thickening, color scale describes the mean score of each group.

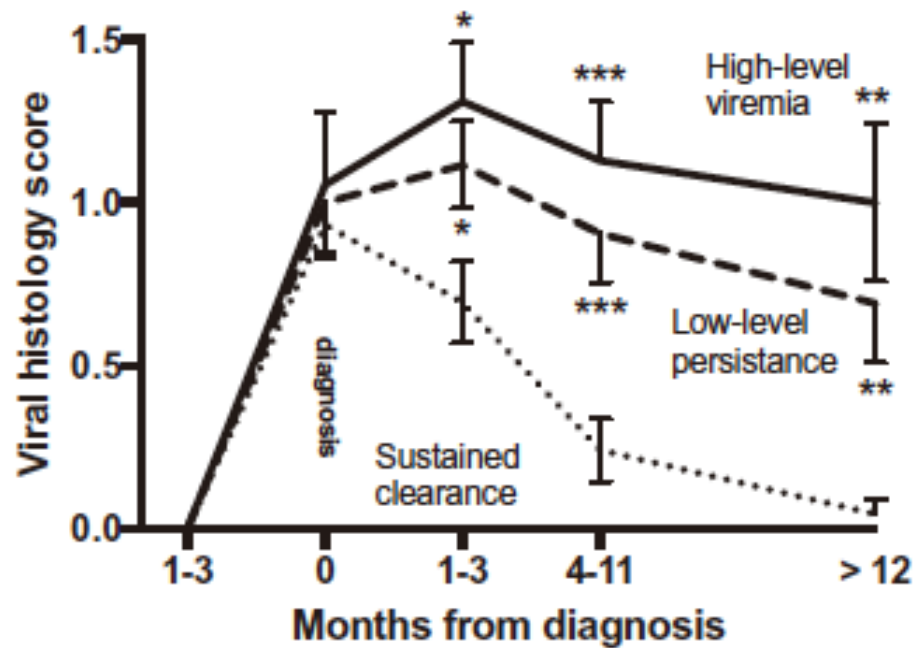
Is improvement of BK nephropathy findings (with serial biopsy) correlated with BK viral load reduction (in blood and/or urine)?

- *Drachenberg et al. (AJT 2004)* n=121/158 biopsies, US
 - 2/11 patients with interstitial fibrosis & tubular atrophy had increased VL → graft loss
- *Drachenberg et al. (AJT 2017)* n=71/206 biopsies, US
 - 76% (54/71) overall, and 80% (48/60) of the patients with functioning grafts cleared viremia (mean 28.2 ± 21.9 weeks after BKVAN diagnosis)
 - 6/6 patients with decreasing VL showed no BKVAN in the second biopsy
 - Poor viral clearance in 8/11 patients with graft loss
 - No clear correlation between pathology and viral clearance but easier identification of H&E cytopathic changes in 5 patients with increasing viremia

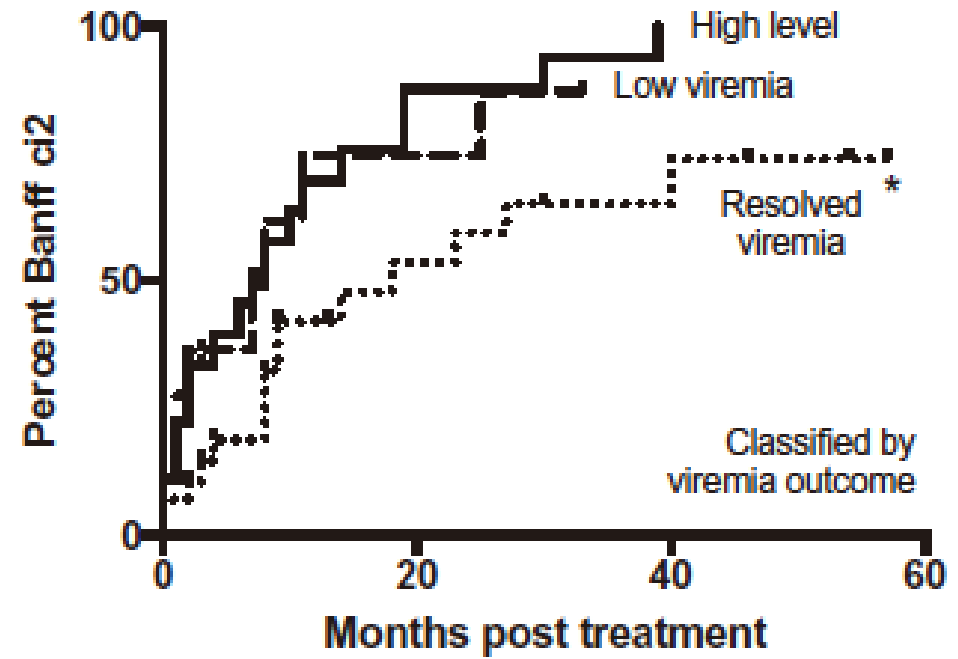
Nankivell et al. (AJT 2017)

n=63 kidney Tx with BKVAN, 453 biopsies,
Australia

Cytopathic effect by viremia outcome



Interstitial fibrosis by viremia



Limitations

HETEROGENEOUS STUDIES

- Studies included were published before the new definition paper - different definitions of BKVAN
- Different definitions of BKVAN proven by biopsy
- Different PCR methods (eg primer)



Any
questions?

