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

1. Does BK DNAemia correlate with BK nephropathy?
2. Does BK DNAuria correlate with BK nephropathy?
3. Does decreasing BK DNAemia correlate with reducing or preventing BK nephropathy?
4. Does decreasing BK DNAuria correlate with reducing or preventing BK nephropathy?
5. 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

- **P**opulation – Kidney transplant recipients of any age
- **I**ntervention – BK DNAemia or DNAuria after transplantation. If samples were stored, studies will also be included
- **C**omparison – No BK DNAemia or DNAuria after transplantation. If all patients included in the study were diagnosed with BKVAN, a comparator was not required
- **O**utcomes – a) If patients with and without BK viremia are included in the study, the primary outcomes recorded will be: BKVAN as defined by the study, BKVAN proven by biopsy, graft rejection, graft loss. b) If all patients included in the study were diagnosed with BKVAN, the main outcome recorded will be improvement of BKVAN findings with serial biopsy with BK viral load reduction in blood and/or urine
- **T**iming – Any time from transplant to outcomes evaluation accepted
- **S**tudy design – observational clinical studies, randomized controlled trials, case series where the total cohort was >10 cases. Conference proceedings if data was considered sufficient eg viral load reported

Exclusion criteria

- Study design: Poster/conference abstract/letters with insufficient data. Case report/case study, reviews, commentary, editorials or opinion articles without original data. Animal studies.
- No quantitative polymerase chain reaction (PCR) eg antigenemia, mRNA, qualitative PCR
- No blood or urine viral load reported
- All patients diagnosed with BKVAN with no serial biopsy and subsequent BK viremia or viruria monitoring
- Only laboratory data without clinical information

Steps

- Step 1 Determine keywords to search articles
- Step 2 Pilot search should be done by librarian
- Step 3 Full search by librarian
- Step 4 Abstract review
- Step 5 Discuss about the discordance between reviewers and decide which articles to full review
- Step 6 Full review (and re-search)
- Step 7 Discuss about the discordance between reviewers and decide which articles to include for systematic review and meta-analysis
- Step 8 Pilot test for data extraction
- Step 9 Data extraction after group meeting

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- Step 8 Pilot test for data extraction – present
- Step 9 Data extraction after group meeting

PRELIMINARY RESULTS

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1. Does BK viremia correlate with BK nephropathy?

- **57** studies were identified
- No BK nephropathy was identified within the non-BK viremia group
- BK nephropathy was observed in a median of **22.22%** (IQR 40.99) patients within the BK viremia group

2. Does BK DNAuria correlate with BK nephropathy?

- **12** studies were identified
- BK nephropathy was identified in the non-BK DNAuria group in a median of 0 (IQR 0) – only 1 study with 10.71% (3/28)
- BK nephropathy was observed in a median of **7.10%** (IQR 22.89) within the BK DNAuria group

Planned analysis

- Planning to identify fold difference in BK VL (blood, urine) between BK nephropathy vs. non-BK nephropathy patients
- Limitations
  - Different timing of BK VL measurements
  - Different specimen (whole blood, serum)
  - Different PCR assays

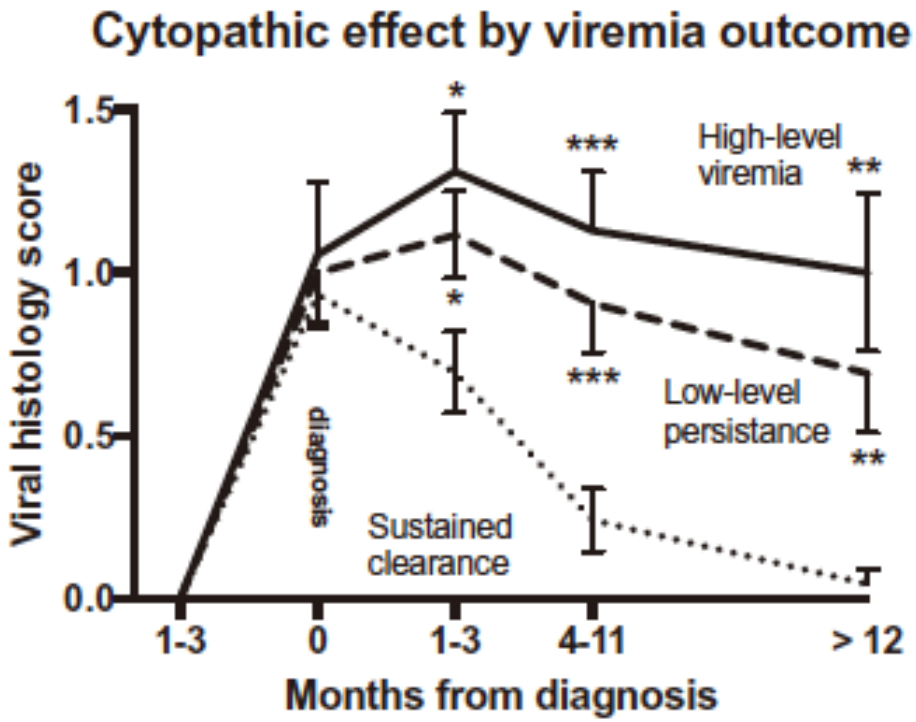
3. Does decreasing BK DNAemia correlate with reducing or preventing BK nephropathy
4. Does decreasing BK DNAuria correlate with reducing or preventing BK nephropathy?

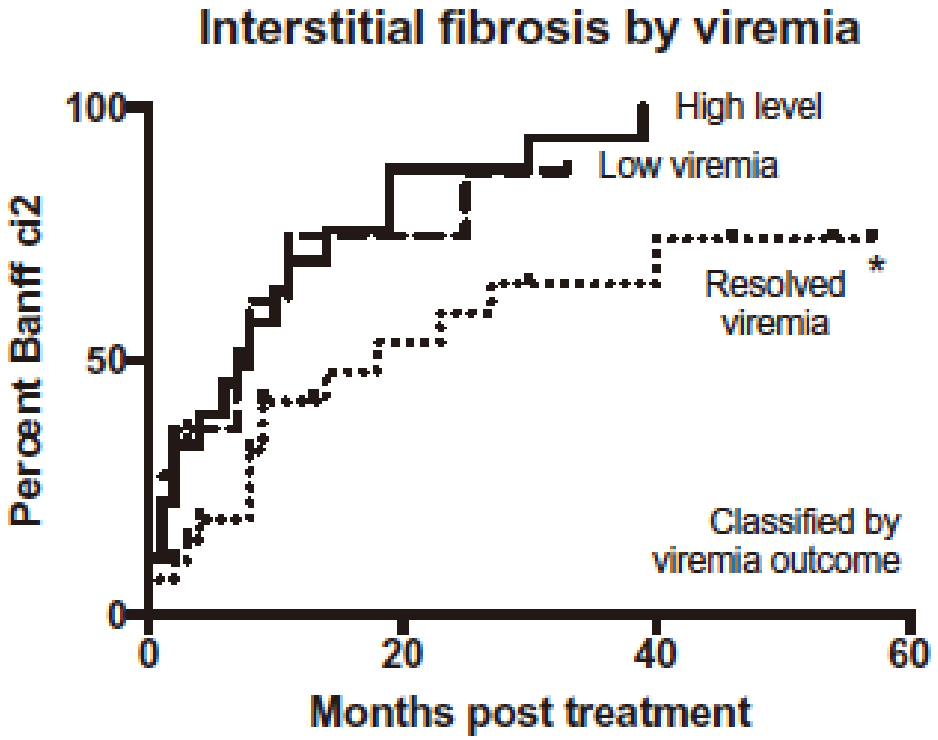
- Undergoing data extraction
- No relevant study to answer these questions so far
- Limitations:
  - Different treatment modalities
  - Different timing/frequency of monitoring

5. 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





Other limitations

HETEROGENEOUS STUDIES

- All studies included were published before the new definition paper - different definitions of BKVAN
- Different PCR methods (eg primer) → to overcome this issue, will try to obtain fold difference
- Different definition of renal dysfunction

Any questions?