

Introduction Digitisation and increasing workload presents an opportunity for artificial intelligence (AI) tools in histopathology. In the UK, approximately 580,000 people live infected with hepatitis B or C and an estimated 30,000 liver biopsies are performed annually in the US. We performed a literature review and analysis to determine understanding of interobserver variation in viral hepatitis grading and staging as a foundation for developing a novel AI tool.

Methods A literature search for papers examining viral hepatitis, interobserver variation and Ishak/Knodell scoring returned 24 papers. Abstracts were reviewed independently with inclusion and exclusion criteria by two consultants and a registrar, and consensus discussion determined the inclusion of eight papers in the final analysis. Average Cohen's kappa coefficient scores of interobserver variation for necro-inflammatory activity (NIA) and fibrosis were gathered and these were used to give a range, mean and weighted mean kappa scores.

Results Results are summarised in the table 1 below. There is poor interobserver variation amongst pathologists, particularly for grading (NIA) of viral hepatitis with mean kappa score 0.33 and weighted kappa score 0.30. Kappa scores for fibrosis showed moderate to substantial agreement (mean kappa score was 0.66 and weighted mean kappa score 0.63. Additional papers noted success with image analysis to improve observer agreement for fibrosis.

Discussion To our knowledge, this is the first review examining interobserver variation of the Knodell and Ishak systems. The results demonstrate where AI can be used to improve agreement between pathologists and therefore provide more consistent pathological assessment for patients.

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IMMUNE-PERFUSION OF LIVER EXTRACELLULAR MATRIX-SCAFFOLDS IN A CUSTOM-MADE BIOREACTOR TO EXPLORE CELL-MATRIX INTERACTION IN LIVER DISEASE

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Liver fibrosis is driven by progressive accumulation of extracellular matrix (ECM), coupled with chronic inflammation. Recent evidence shows that ECM changes in liver disease directly and indirectly modulate the immune system. Since traditional cell culture models often lack immune cell and ECM components, bioengineered models of liver disease using decellularised tissues present an appealing alternative. Here, we describe the generation of a bioengineered model which incorporates the dynamic culture of circulating immune cells with decellularised human liver scaffolds, supported in a custom-made bioreactor to explore interactions between the immune system and liver ECM proteins at different stages of fibrosis.

Liver ECM-scaffolds were generated by decellularising liver tissue with/without underlying disease from human liver tissue samples from partial hepatectomy, or by perfusion decellularisation of whole rat liver using established protocols. PBMCs

isolated from healthy donor whole-blood were first cultured in the bioreactor under semi-continuous perfusion at high (4.22 Pa) or low shear stress (0.34 Pa) and compared to static conditions. Longitudinal profiling of PBMC phenotype was determined by FACs. ECM-scaffold were then perfused with PBMCs and cultured for 5 days. Immune-perfused tissues were stained for PBMC surface markers (T, B, NK cells and macrophages) to identify cell homing.

We designed a custom-made bioreactor which can house 6 decellularised human liver scaffolds and which supports dynamic culture of PBMCs. We found that shear stress impacts PBMC viability and that PBMCs are better supported under low shear stress conditions. PBMC phenotype profiling by FACs show no significant changes in proportion of T cells between static and dynamic culture, while an increase in proportion of Tregs and a decrease in proportion of NK cells were detected in dynamic culture. Perfusion of PBMCs in decellularised scaffolds without fibrosis show homing of cells in different areas of the scaffold at all time points, with CD3+ T cells representing 50% of cells and with small clusters of macrophages, monocytes and B cells at 3 days of culture. Dynamic perfusion improved cell density and homing in decellularised liver scaffolds compared to static conditions.

Our bioengineered system supports dynamic co-culture of PBMCs and decellularised scaffolds, with varying grades of fibrosis, allowing us to explore the interactions between the ECM and immune cells in liver disease in a dynamic perfusion system. A better understanding of ECM-immune interactions will aid our understanding of the driving factors behind fibrosis and could highlight new disease progression biomarkers and therapeutic targets to treat disease.

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LOOKING FOR A NEEDLE IN A HAYSTACK: OUTCOMES OF THE SURREY HEPATITIS C/PHE LOOKBACK EXERCISE. RE-ENGAGING PATIENTS IN A LOW PREVALENCE ODN

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Introduction The World Health Organisation has published a strategy for eradication of Hepatitis C (HCV) by 2030. This will require active case finding and re-engagement of people previously diagnosed with HCV. In September 2018, Public Health England (PHE) and NHS England shared details of patients with historical HCV-positive results from sentinel surveillance between 1996 and 2017, requesting that local operational delivery networks (ODNs) contact each person to retest and treat as appropriate. Here we present the data for the Surrey ODN.

Methods The Surrey 'Lookback' cohort included 1162 people. The PHE protocol was utilised with local amendments. Prior to contacting individuals, cases were cross-checked with NHS spine local databases, paper records and laboratory data to exclude deceased patients and those without active viraemia. The remaining patients received a letter explaining the initiative, followed by up to 3 telephone calls before a final letter

was sent to the GP to advise that engagement was unsuccessful.

Results Of the initial 1162 patients, 241 were assigned to adjacent ODNs, 19 were deceased. Local laboratory systems allowed us to censor 105 patients with negative RNA following initial positive antibody testing. We made contact with 562/797 (70%) of the remaining patients, of whom 100 (12.5%) patients attended for further investigation and were confirmed PCR negative, 149 (19%) reported successful therapy outside the ODN, 21 (3%) reported documented spontaneous clearance, 12 were antibody and PCR negative (1.5%) four of whom categorically denied ever receiving a prior test, and 18 (2%) declined re-engagement. 5.9% of the total cohort were diagnosed with active HCV requiring further treatment (8.4% of the 562 patients we successfully re-engaged). Sadly, one patient was diagnosed with advanced hepatocellular carcinoma as part of work up following re-engagement.

Discussion Initial anxiety about the potential burden of work from the Lookback exercise was unfounded, as many patients were already known to the team or had already received successful treatment. Each telephone contact enabled re-engagement and a discussion regarding new treatment options for those concerned about side effects from previous treatments. We have accounted for 70% of patients, there may be an opportunity to attempt re-engagement of the missing 225 patients at a future date. Some patients were concerned that they were contacted regarding previous investigations, though the majority were happy to have the opportunity to receive treatment if required. We were able to educate and re-engage 47 patients for treatment, with significant personal and population benefits.

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MORTALITY IN PATIENTS WITH WILSON'S DISEASE IN ENGLAND: A NATIONAL REGISTER-BASED STUDY

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Background Wilson Disease (WD) is a rare genetic disorder of copper metabolism. Without appropriate treatment it can progress to liver failure and death. The National Congenital Anomaly and Rare Disease Registration Service (NCARDRS), with support from the Wilson Disease Special Interest Group, has established registration of WD in England. We aim to provide a descriptive study of mortality, including multiple cause of death and transplant status, of those with WD.

Method Confirmed cases of WD were reported by 20 hospital trusts and registered with NCARDRS enabled by their legal permissions (CAG 10-02(d)/2015) to collect patient data without consent. Vital status of all cases were determined and linkage with Office of National Statistics (ONS) mortality data was undertaken to obtain death certificate data. Cases of E83.0 Disorders of copper metabolism, between 2008–2018, were extracted from ONS mortality data. Cause of death free text was manually searched to identify deaths that mentioned WD. All deaths were linked to Hospital Episode Statistics (HES) inpatient data to determine transplant status.

Results Death records were identified for 52 patients, 65% were male, with a mean age of 45.5 years (range 17–82). Complications related to cirrhosis or liver failure were

assigned as the underlying cause of death (UCOD) in 44%. Hepatocellular carcinoma (HCC) was the UCOD in 5.8%. Of the 21% of patients who were recorded as having a liver transplant, transplant complications or graft failure were recorded as a cause of death in 8%. Sepsis was mentioned on the death certificate in 42% and recorded as the UCOD in 21%.

Conclusion The contribution of WD to mortality in England will be underestimated unless multiple cause of death analysis is undertaken. The number of deaths resulting from complications related to cirrhosis or liver failure suggests that there might be missed opportunity for liver grafting. HCC was the cause of death in 5.8% of cases suggesting the prevalence of HCC in WD may be higher than previously thought. This project demonstrates the utility of the NCARDRS' for WD in England.

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PATIENTS WITH SEVERE ALCOHOLIC HEPATITIS (AAH) AND MULTI-ORGAN DYSFUNCTION ADMITTED TO THE INTENSIVE THERAPY UNIT (ITU) HAVE SIGNIFICANTLY WORSE OUTCOMES THAN PATIENTS WITH ACUTE ON CHRONIC LIVER DISEASE (ACLD)

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Introduction Current assumption in the published literature is that AAH is not dissimilar to other forms of ACLF; however, the clinical syndrome of AAH is unique, characterised by profound jaundice and immune dysfunction. Therefore, the outcomes of patients requiring organ support in this setting may differ from other forms of ACLD.

Aim To determine whether the clinical outcomes of AAH patients with multi-organ failure admitted to ITU differ from those with other forms of ACLD.

Method Single-centre retrospective study of consecutive patients admitted to ITU with AAH (AAH ITU) between 10/2014 and 07/2017. Two comparator cohorts were identified - patients with AAH hospitalised but not requiring ITU (non-ITU AAH); and patients with non-AAH ACLD admitted to ITU (non-AAH ITU). The diagnosis of severe AAH was made prospectively adhering to the STOPAH trial criteria, and confirmed retrospectively by two independent Hepatologists; 37% of AAH patients had the diagnosis confirmed histologically.

Results 62 patients were diagnosed with severe AAH during the study period - at the time of hospital admission the median bilirubin was 319µmol/l and 63% had a Glasgow Alcoholic Hepatitis Score ≥ 9 . 21/62 patients were admitted to ITU. AAH ITU patients were more likely to have CLIF-C ACLF (100% vs 80%, $p=0.017$), but had a similar SOFA score ($p=0.064$) and total number of organ supports (2 vs 2, $p=0.447$) to non-AAH ITU patients ($n=70$).

The 90-day survival was 29% for the AAH ITU patients, compared with 90% and 60% for non-ITU AAH and non-AAH ITU patients, respectively ($p<0.001$).

Overall, 15% of AAH ITU and 56% of non-AAH ITU patients who received any organ support survived to hospital discharge. Of the AAH ITU patients with a CLIF-C ACLF grade of 3, 1 patient (8%) survived to discharge, compared with 8/23 (35%) non-AAH ITU patients. Of the AAH ITU patients who required 3 organ support ($n=8$), none survived