Scientific Highlights in Innovation

The following scientific highlights have been selected to showcase key findings across a selection of therapeutic areas.

Long-term Consequences of COVID-19: 6 Months On

COVID-19 took the world by surprise in late 2019, pushing scientists to study the virus extensively and create an effective vaccine. Despite the numerous hours, weeks, and months of research there remains a lot that is not well understood about the deadly virus. The long-term health consequences of COVID-19 remain a mystery to doctors and not all risks are clear. Scientists in Wuhan, China, aimed to determine what some of the long-term consequences of COVID-19 were by conducting a large cohort study and assessing disease severity.

The study took place from January 2020 to May 2020 and involved a cohort of patients with COVID-19 discharged from Jin Yin-tan Hospital, Wuhan, China. Patients who had died before the follow-up, had been re-admitted, or had been discharged due to other conditions were not included in this study. In total, 1,733 patients were enrolled in the cohort study; 52% of this sample were men and the median age of patients was 57 years. Each participant underwent a series of questionnaires to assess their symptoms and quality of life.

Further to this, all patients had a physical examination, took part in a 6-minute walking test, and received blood tests. Methods used included a stratified sampling procedure to categorise patients as 3, 4, and 5–6 according to their highest seven-category scale during their stay at the hospital. Statistical models, namely a logistic regression model and a multivariable-adjusted linear model, were conducted to assess the link between disease severity and long-term consequences.

Findings revealed that fatigue and muscle weakness were the most common symptoms, found in 63% and 26% of patients, respectively. Additional findings uncovered that the mental health of 23% of participants was also affected, particularly resulting in anxiety and depression. The walking test demonstrated that 29% of patients had a walking distance less than the lower limit of the normal range and high severity scale result (5–6); 56% of these patients also had impairment of pulmonary diffusion.

The authors concluded that the most debilitating symptoms in patients with COVID-19 6 months after acute infection were fatigue, muscle weakness, sleep difficulties, anxiety, and depression. The more ill the patient was during their hospital stay correlated with the patient having more severely impaired pulmonary diffusion and atypical chest imaging manifestations. Overall, this study highlighted the importance of following up with severely ill patients with COVID-19 and providing long-term care after the initial COVID-19 infection. ∎

Reference

Huang C et al. 6 Month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021;397(10270):220-232.

Randomised Trial Supports Hypothermic Oxygenated Machine Perfusion in Liver Transplantation

ACCORDING to recent findings, there is increased risk of complications of a biliary nature in liver transplantation when using livers obtained after circulatory death. A new study in a field with limited comprehensive research has revealed that hypothermic oxygenated machine perfusion leads to a lower risk of non-anastomotic biliary strictures, superior to conventional static cold storage. The use of the *ex situ* machine perfusion method shows real promise and would be integral to improving outcomes after organ transplantation. The ongoing study by van Rijn et al. has already been highly cited, reflecting the interest shown by many clinicians and their patients in this encouraging evidence.

In this multicentre, controlled trial, transplant patients were randomly assigned to receive their liver after either oxygenated machine perfusion or conventional static cold storage. The primary endpoint for both the machine-perfusion group and the control was the incidence of non-anastomotic biliary strictures within 6 months. There were 160 participants enrolled in the trial, with 78 receiving machine-perfused livers and 78 receiving livers from static cold storage (four did not receive a liver). Non-anastomotic biliary strictures occurred in 6% of patients in the machine-perfusion group and 18% of the control group, whilst 12% of the machine-perfusion group experienced post-reperfusion syndrome compared with 27% in the control group. Moreover, early allograft dysfunction was seen in 26% of the machine-perfused livers versus 40% for the static cold storage livers. Incidence of adverse events was similar across both branches.

When compared to conventional methods of preservation, those randomly assigned to receive machine-perfused liver grafts had a risk lower by two-thirds of developing symptomatic non-anastomotic biliary strictures within 6 months of transplantation. This protective trend was also exhibited in the lower risk of post-reperfusion syndrome and early allograft dysfunction. Moving forwards, the prevention of post-transplantation cholangiopathy in this way may not only increase the acceptance rates of liver grafts, but also improve the cost effectiveness of machine perfusion. The authors recognised that larger trials are warranted to detect an effect on survival rates after liver transplantation and risk of graft loss. ∎

Reference

van Rijn R et al. Hypothermic machine perfusion in liver transplantation. N Engl J Med. 2021;384(15):1391-1401.

"hypothermic oxygenated machine perfusion leads to a lower risk of non-anastomotic biliary strictures, superior to conventional static cold storage"
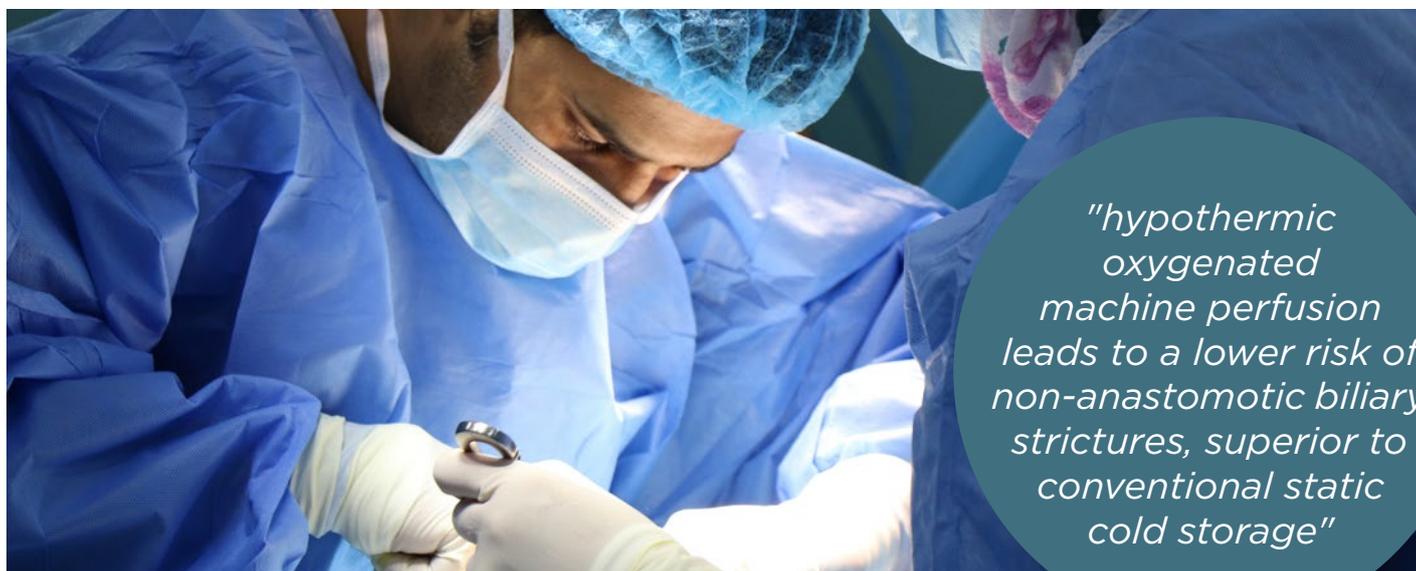
Artificial Intelligence-Based Differential Diagnosis for Cancers of Unknown Primary

MODERN cancer therapeutics such as chemotherapy and immune checkpoint inhibitors are now highly targeted and often specific to the primary tumour in each case. Cancer of unknown primary (CUP) refers to a group of cancer diagnoses where the primary anatomical site of tumour origin cannot be determined, thus creating significant challenges with targeted therapies. In many cases, the primary is never determined even after extensive diagnostic work-up, which is both time- and resource-consuming and significantly delays the administration of appropriate treatment.

Researchers from Harvard Medical School, Boston, Massachusetts, USA, investigated the use of a deep-learning-based computational pathology algorithm called the Tumour Origin Assessment via Deep Learning (TOAD), which can be used to analyse histology slides and provide differential diagnosis for CUP. The multi-task deep model was educated using slide images of known primary tumours, spanning 18 common tumour origins. The model was subsequently tested in 4,932 cases of known origin, achieving an accuracy of 0.84 in both the malignancy classification and the identification of primary tumours. In external tests with images from other hospitals, the model achieved an accuracy of 0.79. The external tests allowed the researchers to test the adaptability of the model across different healthcare systems who use different histological sample preparation standards. Previous studies have demonstrated that pathologists often struggle to identify the origins of metastatic tumours when minimal clinical information is available. This model demonstrated the ability to make fairly accurate primary differentials even for challenging metastatic cases using only histology with patient gender data.

The proposed model represents a novel assistive tool to be used in complicated CUP cases. With future research, this could be used in conjunction with or instead of immunohistochemical analysis and extensive diagnostic work-up to reduce the occurrence of CUP. ∎

Reference

Lu MY et al. AI-based pathology predicts origins of cancer of unknown primary. Nature. 2021;594(7861):106-10.

"The model was subsequently tested in 4,932 cases of known origin, achieving an accuracy of 0.84 in both the malignancy classification and the identification of primary tumours."

EVOQUE Tricuspid Valve Replacement System for Severe Tricuspid Regurgitation

> *"although all patients were at high surgical risk and initially had an NYHA Class of III or IV, technical success was at 92% with 0 deaths occurring during surgery"*

TRICUSPID regurgitation (TR) is a condition where the valve between the right atrium and right ventricle does not close properly, causing blood to flow back into the atrium. Approximately 85% of adults may experience mild TR; however, issues arise when the condition is severe, causing distressing symptoms such as swelling of the abdomen, shortness of breath, and fatigue. One viable treatment option is transcatheter leaflet repair, although this might not be suitable for all; transcatheter tricuspid valve replacement (TTVR) may be a more appropriate option for a larger number of patients. This novel study, detailing a first-in-human experience of TTVR, aimed to investigate the safety and practicality of EVOQUE TTVR for treating patients with severe TR.

The lead authors of this study, Niel Fam, St. Michael's Hospital, University of Toronto, Ontario, Canada, and Ralph Bardeleben, Universitätsmedizin Mainz, Johannes Gutenberg Universität, Germany, shared their findings of this first-in-human experience testing EVOQUE TTVR. Scientists recruited 25 patients with severe TR, who were predominantly female with a mean age of 76 years, to undergo EVOQUE TTVR. The primary outcome was the technical success of the procedure, with consideration to the New York Health Association (NYHA) classification, TR grade, and severe adverse events at 30-day follow-up.

Results showed that, although all patients were at high surgical risk and initially had an NYHA Class of III or IV, technical success was at 92% with 0 deaths occurring during surgery. Additional findings demonstrated that at the 30-day follow-up there was 0% mortality, NYHA functional class was lower at I or II in 76% of patients, and 96% of patients had a TR grade ≤2+. Adverse events included major bleeding in three patients, two patients needing dialysis treatment, and one patient requiring pacemaker implantation.

Overall, this study demonstrated the effectiveness of EVOQUE TTVR in this first-in-human procedure. The results showed that EVOQUE TTVR has high technical success, significant clinical improvement, and few severe adverse events. Fam and Bardeleben acknowledged their small sample size as a limitation and suggested that larger studies are needed to confirm safety and long-term clinical outcomes. ∎

Reference

Fam NP et al. Transfemoral Transcatheter Tricuspid Valve Replacement with the EVOQUE System: A Multicenter, Observational, First-in-Human Experience. JACC Cardiovasc Interv. 2021;14(5):501-11.

Adverse Obstetric and Perinatal Outcomes Compared in Programmed and Natural Cycle Frozen Embryo Transfer

OBSERVATION of singleton deliveries in Denmark has revealed how the outcomes of pregnancies differ with contrasting frozen embryo transfer (FET) protocols.

Asserhøj et al. performed a register-based study including all singleton deliveries after assisted reproductive technology in Denmark between 2006 and 2014. Outcome measures were assessed in the 1,136 deliveries, grouped by FET protocol into programmed FET (n=357), modified natural cycle FET (n=611), and true natural cycle FET (n=168). The obstetric outcomes assessed were hypertensive disorders in pregnancy, pre-term pre-labour rupture of membranes, placenta praevia, placental abruption, induction of labour, postpartum haemorrhage, and caesarean section. Meanwhile, the perinatal outcomes assessed were post-term birth, pre-term birth, birth weight, small for gestational age, and large for gestational age.

The study findings identified a significantly higher risk of hypertensive disorders in pregnancy, postpartum haemorrhage, and caesarean section after programmed FET compared with natural cycle FET (both modified and true natural cycle). A higher risk of experiencing birthweight >4,500 g was also observed in programmed FET versus natural cycle FET. Based on this study, the authors were able to conclude that programmed FET adversely affected both obstetric and perinatal outcomes. On the back of this discovery, the investigators recommended, where possible, endometrial preparation with the creation of a corpus luteum.

Moving forwards, randomised control trials of FET that compare programmed and natural cycles are warranted to clarify and further this research. Broadening the catchment area and participant recruitment requirements to include a more varied population will also benefit applicability of these findings. ∎

Reference

Asserhøj L et al. Adverse obstetric and perinatal outcomes in 1,136 singleton pregnancies conceived after programmed frozen embryo transfer (FET) compared with natural cycle FET. Fertility and Sterility. 2021;115(4):947-956.

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