CHAPTER 6

CONCLUSIONS AND FUTURE RECOMMENDATIONS

6.1 Conclusions

This study is the first of its kind in Malaysia that explores differentially expressed genes in high-risk cardiac surgery patients who develop POCD. Interesting findings from this study include the involvement of immunoregulatory genes in the subjects. This strengthens the idea that immune responses are responsible for POCD development, specifically in NK cells mediated cytotoxicity pathway. Even though KIR genes involved in a small part of the whole pathway, the significant downregulation proves that it does affect POCD.

Another important finding is that the upregulation of ERFE genes in the POCD subjects. Erythroferrone was highly involved in red blood cell production to compensate for the decrease in blood volume after the surgery. In accord with the molecular finding, the serum ERFE level also found to be significantly high in POCD patients. This suggest a potential use of serum ERFE in detecting early POCD. This is a novel finding that correlate ERFE in cognitive-related conditions. This shows the difference between ERFE level in POCD and non-POCD groups, allowing us to utilizes ERFE as potential biomarker. Utilizing cerebral oximetry has caused genes MORN4, CCL23 and GPR37L1 to be downregulated. They are genes related to neuronal damages. Hence, their downregulation in patients using cerebral oximetry helps in ameliorate brain injury, as well as reducing risk for POCD.

The novelty of this study is that we are able to prove the involvement of few least discussed genes that are associated to different outcomes of cardiac surgery specifically POCD. The genes that were found were coding genes, that is crucial for further discovery and application of protein biomarker. For example, the ERFE protein in this study could be explore in depth to its application in predicting POCD.

6.2 Limitations

This study has a few limitations that can be improved. Firstly, the level of erythroferrone for protein biomarker in this study is based on 88 patients in our population. The ROC curve generated reflecting only on these particular patients. In order to use this ERFE level as the reference for POCD diagnosis, a larger sample are needed to be tested, hence producing a more robust result. In term of RNA samples, the analysis was done in batch, according to comparisons. The second batch of the samples were poorly handled, causing the RNA to be degraded and loss its quality. Hence, the samples were discarded, leaving a limited number of RNA samples available for analysis.

For usage of cerebral oximetry, the randomisation was based on clinical judgement of the anaesthesiologist. Since there were multiple anaesthesiologist involved across the study, the randomisation is varied. Up to date, there were no specific guide to use cerebral oximetry perioperatively. Having a specific guideline is recommended to ease operative planning, risk analysis and cost management of a patient.

Other than that, current study involved specifically high-risk patient settings. In overall setting that includes both of low and high-risk patients, the results may differ.

Hence, by including all patients in future study, a comparison can be made on the gene expression level and protein biomarker level.

6.3 Recommendations

This study needs further improvement in the future. For example, this study needs to be replicated using more POCD patients to confirm the DEGs relation with POCD. This will give a robust result and perhaps completes the disparity from this study. Then, further analysis on pathway and network could be mapped clearly. This will elucidate how specific mechanism, such as immunoregulatory and iron metabolism that we found, actually contribute to POCD. With that knowledge, we are able to target specific pathway or process to improve POCD, either by medication, intervention or postoperative management.

Apart from that, the current study also gives a promising result, especially in biomarker study. We strongly suggest utilizing ERFE as a biomarker to predict the occurrence of early POCD. A cross-sectional study involving a wide range of POCD and non-POCD patients could be done to assess the feasibility of serum ERFE level in becoming a predictor for POCD. We are also keen to know if serum ERFE level preoperatively can use to foresee POCD. A similar study might be done, with additional timepoint of serum ERFE level measurement. This may include pre-, intra- and postoperative ERFE, as well as assessment of early and late POCD.

Other than that, researchers can use other molecular test to detect mutations. Since POCD is actively studied in molecular level, we can utilize technology to identify any specific mutations that may occur in development of POCD. In this case, usage of next-generation sequencing (NGS) is highly recommended to provide extra information on

disease-related mutations. Till now, POCD study only reach up to gene expression analysis. There is a huge opportunity for researchers to explore this field as POCD is a complication that yet to a solution.