Chapter 1: Introduction

1.1. Background

Dengue is a prominent mosquito-borne viral disease in both tropical and subtropical areas, which are optimal for mosquito breeding. Dengue virus (DENV) is an infectious agent of dengue disease and four DENV serotypes (DENV-1 to DENV-4) have been identified based on the cross reactive assay (Sucipto et al., 2018). Despite the differences, infection by any of the serotypes still causes the same disease and clinical manifestations. Clinical manifestations of dengue extend from dengue fever (DF), to more severe stages, such as dengue shock syndrome (DSS) and dengue hemorrhagic fever (DHF) (Martina et al., 2009). Dengue is considered as a significant public health concern with approximately more than 390 million reported cases worldwide (Bhatt et al., 2013). Indonesia, which has a tropical climate, is considered as one of the most dengue prevalent countries in the world (Nusa et al., 2014). In 1968, dengue outbreak occurred for the first time in Surabaya and Jakarta (E Setiati et al., 2006). Since then, cases of dengue fever have spread to every region of Indonesia with an increasing number of reported cases. All four DENV serotypes circulate in entire provinces of Indonesia and cause dengue disease every year with occurrence of major outbreaks periodically (Fahri et al., 2013; Nusa et al., 2014).

The severity of dengue caused by each DENV serotype varies from asymptomatic to lethal diseases (WHO, 2009). Previous studies shown that the presence of NS1 (Non-structural 1) protein contributes to disease severity of dengue patients (Martínez-Cuella et al., 2020; Paranavitane et al., 2014). NS1 is an extremely conserved non-structural protein of DENV that has various importance for survivability and pathogenicity of DENV. Intracellular NS1 assumes a dimer form and is crucial for genome replication, while secreted NS1 assumes a hexamer form and is crucial for immune avoidance (Rastogi et al., 2016). Secreted NS1 is also known to contribute to several common clinical manifestations in DHF and DSS patients, such as vascular leakage, thrombocytopenia, and coagulopathy. NS1 has been shown to cause hyperpermeability in human endothelial cells through its interactions with the endothelial glycocalyx layer (EGL) and consequently causing vascular leakage

that can lead to shock and even death. Therefore, vascular leakage is considered as a crucial determinant of dengue severity (Puerta-Guardo et al., 2016).

In Indonesia, all DENV serotypes were distributed in almost all regions and each serotype also cause dengue with different disease severity. DENV-3 was reported to cause the most cases of severe dengue disease in Indonesia (E Setiati et al., 2006). This might suggest that NS1 protein of DENV-3 in Indonesia have different amino acid composition and structure compared to other serotype, which increase the chance of triggering vascular leakage and cause severe dengue disease. Therefore, analysis of NS1 amino acid sequence and structure of all DENV serotypes in Indonesia will provide more insight and understanding of amino acid composition and structure of DENV NS1.

1.2. Objectives

The objective of this study is to analyze the amino acid composition and structure of DENV NS1 protein in Indonesia in order to observe the differences between each serotype and investigate its relation to cause hyperpermeability in severe dengue disease. The amino acid composition and structure of the DENV NS1 protein will be examined and analyzed using UCSF Chimera software.