The systemic inflammatory response syndrome (SIRS) is a major cause of morbidity and mortality. SIRS is thought to be due to an over amplification of inflammatory cytokines. Toll-like receptor 4 (TLR4) is a transmembrane receptor that recognises lipopolysaccharide. The TLR4 Asp299Gly polymorphism has been shown to reduce lipopolysaccharide responsiveness. We examined whether this TLR4 polymorphism is associated with severity of SIRS. We conducted a cohort study of patients with SIRS on the general ITU ward. DNA was genotyped using a tetra-primer ARMS-PCR and genotypes were compared to phenotypic outcomes. 94 patients (mean age 57 y) were recruited. The genotype frequencies were Asp/Asp 91.5%, Asp/Gly 7.4% and Gly/Gly 1.1%. The frequency of the Gly/Gly or Asp/Gly genotype was increased in SIRS patients who died in ITU as compared to those who survived (19% versus 5%, p=0.076, Fisher’s exact test). There was no association with other severity indicators. The trend towards increased mortality in those carrying the Gly allele possibly suggests a role for TLR4 signalling in the severity of SIRS. Recruitment is ongoing to increase the sample size to confirm this result.