In malaria-endemic regions of western Kenya, *Plasmodium falciparum* malaria manifests clinically as severe malarial anemia [SMA; hemoglobin (Hb) <6.0g/dL, with any density parasitemia]. The induction of prostaglandin (PG)-E2 production through cyclooxygenase (COX; prostaglandin-endoperoxide H synthase) pathway is an important host-defense mechanism against infective agents. Although previous studies have shown that PGE2 concentrations, COX-2 transcripts and protein levels are reduced in children with severe malaria, the impact of *in vivo* malaria pigment-containing monocytes (PCM) on systemic PGE2 production and COX-2 mRNA expression in children with SMA remains unexplored. In addition, no studies to date have reported the association between COX-2 genetic variation and susceptibility to SMA. As such, plasma and urinary PGE2 (measured as the stable end metabolite: bicyclo-PGE) levels and COX-2 mRNA transcripts were investigated in children (n=74; age<36 months) categorized into non-SMA (Hb<6.0g/dL, with any density parasitemia; n=38) and SMA (n=36), presenting at Siaya District Hospital, western Kenya. In addition, the association between promoter variants COX-2 -512 C>T(rs20420), -608 T>C (rs20419), -765 G>C (rs20417), -1132 G>A (rs20415) and -1195A>G (rs689466), and susceptibility to SMA were investigated among parasiticemic children (n=842) participating in the same study. The results revealed significantly decreased plasma (P=0.001) and urinary (P<0.001) bicyclo-PGli, levels and COX-2 mRNA transcripts (P=0.007) in children with SMA relative to non-SMA. Furthermore, decreased plasma bicyclo-PGfi, levels were associated with insufficient erythropoiesis (reticulocyte production index; RPI<2.0, P=0.026), and an increasing number of pigmented monocytes (PCM) in plasma (P=0.031) and urine (P=0.070). Additionally, COX-2 mRNA transcripts decreased with increasing levels of PCM (P=0.026). Analysis of co-infections in malaria demonstrated significantly lower plasma bicyclo-PGE2 levels in children with both malaria and HIV-1 or bacterial *Pf (+)* HIV-1 (+) Bac. (+), relative to children with falciparummalaria mono-infection [*Pf (+)] (P<0.001). In addition, COX-2 mRNA transcripts were decreased in children with [*Pf (+)* HIV-1 (+) Bac. (+)] (P=0.023). Analyses of COX-2 promoter polymorphic genotypes and their haplotype constructs using binary logistic regression modeling, controlling for confounding effects of age, gender, sickle cell trait, HIV-infection and exposure, G6PD deficiency, α+ thalassemia and bacterial infections, led to no effect of individual genotypes on SMA. However, carriers of the -512 CI -608CI_e7v6e5aCI _1195A (CCCA) haplotype were protected against SMA (P=0.043) and presented with increased plasma bicyclo-PGE2 levels (P=0.011). By contrast, carriers of the TTGG haplotype were at an increased risk of developing SMA (P=0.077). Similarly, carriers of the_608C/-765C (CC) haplotype had a 73% reduced risk of developing SMA (P=0.037) and increased plasma (P=0.011) and urinary (P=0.045) bicyclo-PFils, levels. However, carriers of the TG haplotype were at an increased risk of developing SMA (P=0.062) and presented with lower urinary bicyclo-PGE2 levels (P=0.001) and COX-2 mRNA transcripts (P=0.025). Taken together, these results illustrate that COX-2 mRNA expression is downregulated in children with SMA, and associated co-infections, resulting in decreased invivo PGE2 production, driven at least in part, by naturally acquired *Plasmodium* pigment (hemoglobin) by monocytes. COX-2 derived PGE2 is also regulated by promoter variant that may impact on erythropoiesis, and thereby, influence the development of SMA.