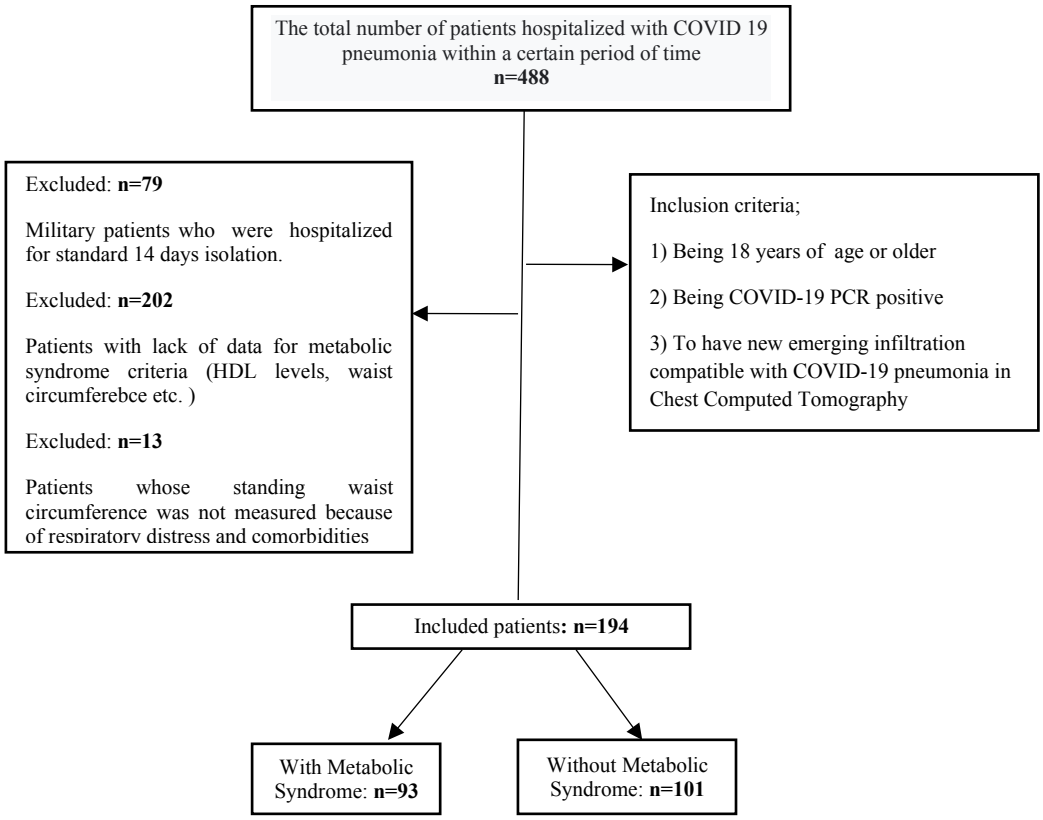Figure 1. Study design and population