

Modeling of Liver Cancer Risk Factors and Dynamics at Community Level

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Abstract

Hepatocellular carcinoma (HCC) is a malignant cancer of the liver arising from uncontrolled multiplication of the abnormal liver cells. It is an ignored public health condition where patients come late to the hospital at terminal stages. Its development is preceded by liver inflammation arising from the risk factors of HCC affecting the liver. HCC is one of the few cancers with both infectious and non-infectious causes. The common causes range from infections with viral hepatitis B and C and non-infectious conditions which include excess alcohol intake, aflatoxins, iron overload, genetic pre-disposition, environmental factors, obesity, and about 18% are of unknown causes. While HCC has been observed in HIV positive persons, it is known that HIV alone cause liver inflammation but there is no direct causal relation with HCC. A model based on a system of differential equations has been formulated to investigate the impact of the HCC infectious risk factors and HIV on the dynamics of HCC. The existence of the stable steady equilibrium states was determined with respect to the reproduction number R_0 derived using the next generation matrix approach. Stability analysis of the model

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was done to determine the condition for the spread and magnitude of the HCC as a result of the infectious risk factors. Numerical simulation was done using MATLAB software to graphically illustrate the effect of the risk factors on the dynamics of the HCC in the community. The findings of this study provides healthcare workers and stakeholders with knowledge on liver cancer dynamics and this could be used to improve on prevention of HCC and formulation of policy on HCC prevention and management.

Keywords: Modeling, Liver-cancer, Risk factors, Community

1 Introduction

Hepatocellular carcinoma (HCC) is a malignant cancer of the liver, the second largest organ of the body. It is a primary liver cancer derived from primary liver cells and represents the sixth most common neoplasm and the third leading cause of cancer-related mortality world-wide [1,2]. Common risk factors for HCC include both hepatitis B and C viruses, aflatoxins, excess alcohol intake, iron overload, obesity, genetic predispositions, and 18% of cases are of unknown causes [3, 4]. In the developed world, obesity is increasingly being recognised as a main risk factor of HCC [5, 18]. In many regions of the sub-Saharan Africa (SSA), HCC is a public health problem which is ignored, often under diagnosed or diagnosed when too late. Its occurrence has a clear geographical distribution, having the highest incidences in East Asia, SSA and Melanesia, where about 85% of all cases occur due to the high prevalence of hepatitis B virus (HBV) infection in these regions [3, 18], while hepatitis C virus (HCV) is prevalent in the developed countries [1, 19]. HBV is endemic in Western Kenya at 5-8% [15].

Cancers including HCC are the number four killer disease in Kenya after Malaria, Pneumonia, and HIV/AIDS [9, 12]. HIV is prevalent in Western Kenya and is known to independently cause liver inflammation, which is a precursor to the development of HCC but its relevance in actiopathogenesis of HCC is not clear. A number of mathematical models of liver cancer have been formulated but none has incorporated the risk factors. In this study a mathematical model was developed objectively to depict the effect of infectious risk factors of HCC and their dynamics in the community. The model will also delineate the relevance of HIV in causation of HCC. This predictive analysis modeling can effectively elucidate this and inform policy on prevention of HCC.

2 Materials and Methods

The study was approved by the institution review board of Jaramogi Oginga Odinga Teaching and referral Hospital Kisumu. The study site was Kisumu county hospital liver clinic and medical wards. Informed, signed consent was obtained from each subject, (<18 years old signed by parent(s) or guardian). Using data collected from June 2015 to June 2016 which included 331 (241 males and 90 females) subjects, 257 (178 males and 79 females) subjects with hepatocellular carcinoma were included into the study. 74 (50 males and 24 females) subjects, had liver mass which were not HCC and were excluded. A standard questionnaire was administered for each study subject and it included: The patients baseline information: demographics:- bio-data (age in years, sex (M/F)), weight (Kg), height (cm), symptoms and signs of HCC, duration of abdominal swelling and family history of HCC. Each study subject underwent a physical clinical examination. Under aseptic technique, blood was drawn from the cubital fossa and used to determine the following tests to identify the risk factors of HCC and included triple serology for HBV, HCV, HIV, for viral markers HBsAg, anti-HCV and HIV-antibodies, alpha-fetoproteins, biochemistry (ALT, AST), *CD4+* cell counts, urine for aflatoxins and ultrasound of the abdomen was also done for each study subject. The risk factors associated with HCC in the study were identified and used to determine the mathematical model to illustrate their dynamics in the community. ALT-alanine transaminase, AST-aspartate transaminase, BMI-body mass index, BCLC-Barcelona Clinic Liver Clinic, AFP-alphafetoproteins.

3 Model Description and Analysis

3.1 Model Description

The model subdivides the human population into classes of susceptible and the infected with the risk factors and the HCC as;

$$N(t) = S(t) + I(t)$$

At any time t new recruits enter the population through birth and migration at constant rate Λ_H . S_H are those individuals that are susceptible to the risk factors, B and C are the persons who are infected with hepatitis B and hepatitis C virus respectively. O represents those who are susceptible to obesity, I are the HIV infected individuals and T are the aflatoxins affected persons, X_I are the individuals whose liver is at the inflammation stage from all the risk factors, X_H are the HIV infected people whose liver is at inflammation stage,

Table 1: Summary of baseline characteristics: Socio-demographic, Clinical and laboratory profile of the 257 study subjects.

Parameter	Mean± SD, (%)
M:F ratio	2.1 : 1
Mean age (years)	46.2± 25.1 (range 15-80)
CD4+ cell count (350-1600)cells/μl	237.7±96.4[range 50-417]
Mean CD4+ cell counts[mean± SD]	
CD4+ > 500	15(13.9%)
CD4+ (350-499)	10 (9.3%)
CD4+ (200-349)	52 (48.1%)
CD4+ < 200	31 (28.7%)
BIOCHEMISTRY (Mean ± SD)	
ALT (5-37 IU/L)	193.5 ± 215.9 [range 2.9-1327]
AST (5-40 IU/L)	173.0± 142 [range 14-600]
AFP (0-9 ng/ml)	14,205± 215.9 [range 0.5-433,879]
HCC and	
HBV mono-infection	40 (13.2%)
HCV mono-infection	1 (0.38%)
HIV mono-infection	51 (19.8%)
HBV/HIV co-infection	58 (22.56%)
HCV/HIV co-infection	0 (0%)
HCC No risk factor/HIV	93 (36.1%)
Excess alcohol intake	7(2.7%)
BMI (obesity > 30.0)	5 (1.9%)

X_C are the individuals at the cirrhosis stage, Y_C are those with liver cancer at terminal stage of HCC. Susceptible individuals become alcoholic at the rate Ψ_1 . Similarly susceptible people acquire hepatitis B virus at the rate

$$\Psi_2 = \frac{(\theta\zeta B + \varphi\alpha_b B + \gamma\rho X_i)}{N}$$

where ζ accounts for high rates of infection due to large numbers of hepatitis B infected people and φ the likelihood that HBV infected persons at inflammation stage will cause more infection. Individuals acquire hepatitis C virus

Aflatoxins (1.0-5.0 ppb)	8.35 ppb [2(0.77%)]
Positive family history of HCC	5(2%)
BCLC Staging for HCC.	
O	0 (0%)
A	5 (1.9%)
B	37 (14.4%)
C	90 (35.1%)
D	125 (48.6%)
Duration-Abdominal swelling (Months)	3.6 ± 2.66 [range 1-8]

at Ψ_3 , where

$$\Psi_3 = \frac{(\theta C + \eta \alpha_C C + \gamma \rho X_I)}{N}$$

where η is the transmission probability of Hepatitis C and is less than ψ because of the low hepatitis C infection in Kenya and θ accounts for high rates of infection at acute phase because the body has not adjusted to fight the virus and because of the asymptomatic nature of HBV and HCV infection many people are unaware of their infective status and the rate at which HIV is acquired at Ψ_4 where;

$$\Psi_4 = \frac{(\xi I + \omega \alpha_i I)}{N}$$

ξ is the modification parameter that accounts for increased likelihood of infection by highly infectious HIV infected persons, and ω is the probability of acquiring HIV from infected persons at inflammation phase.

3.2 Assumptions

- (i) One only gets infected by a single risk factor.
- (ii) Death due to disease only occurs at the final stage of HCC.

Table 2: Variables

Variable	Explanation
S_H	The Susceptible individuals
O	The obese individuals
A	The alcoholics
B	The HBV infected
C	The HCV infected
I	The HIV infected
T	The aflatoxins affected/infected
E	The environment affected
X_I	All the infected at inflammation stage
X_H	The HIV infected at the inflammation stage
X_C	Those at the cirrhosis stage
Y_C	The individuals at HCC stage

Table 3: Parameters

Parameters/ Rates	Description
Λ_H	Rate of recruitment into susceptible individuals
μ	Natural mortality rate
Ψ_1	Rate at which the susceptibles become alcoholic
Ψ_2	Rate at which the susceptibles get infected with HBV
Ψ_3	Rate at which the susceptibles get infected with HCV
Ψ_4	Rate at which the susceptibles get infected with HIV
Ψ_5	Rate of getting affected by aflatoxins
Ψ_6	Rate of susceptibles getting affected by the environment
Ψ_0	Rate at which susceptible are predisposed to obesity
α_1	1
$\alpha_0, \alpha_a, \alpha_b, \alpha_c$ $\alpha_I, \alpha_e, \alpha_g$	Rate at which the infected persons move to inflammation stage due to obese aflatoxins, HBV, HCV, HIV, environment and genetically predisposed respectively
ρ	Rate of inflammation to cirrhosis
σ	Rate at which one progresses to HCC.
Ω	HIV inflamed to HCC
θ	High rate of infection with HBV and HCV at acute stage

3.3 Variables

3.4 Parameters

3.5 Flow diagram

From the above definitions and explanations the following model has been developed.

$$\frac{dS_H}{dt} = \Lambda_H - \mu S(t) - \Psi_0 S(t) - \Psi_1 A(t) - \Psi_2 B(t) - \Psi_3 C(t) - \Psi_4 I(t) - \Psi_5 T(t) - \Psi_6 E(t),$$

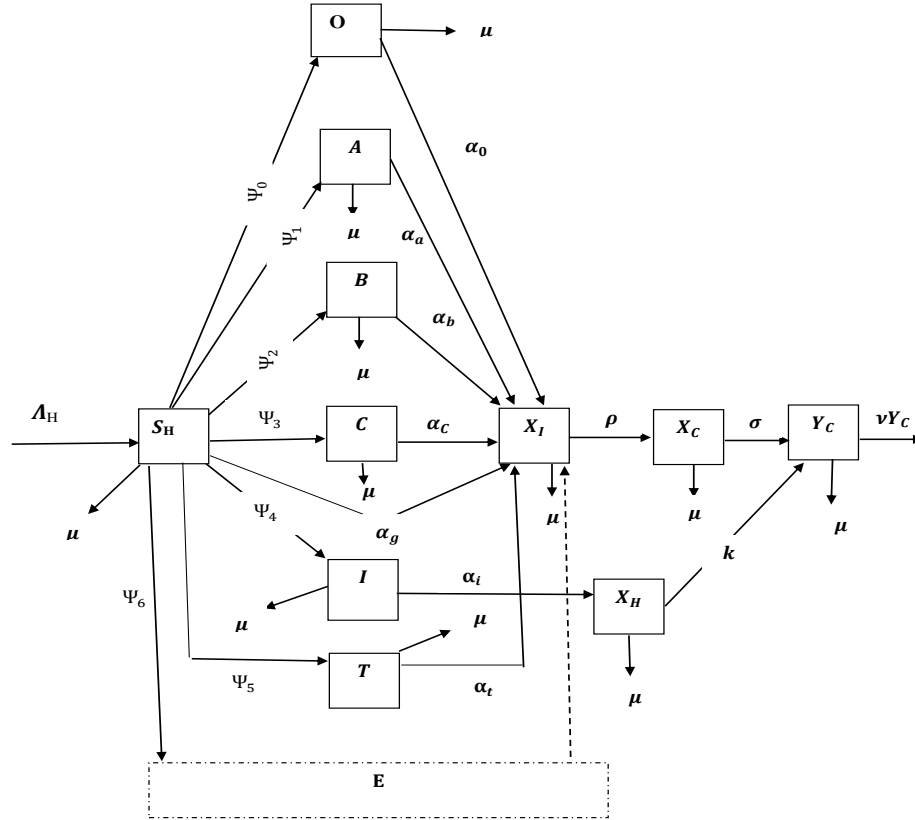


Figure 1: Model flow compartmental diagram

$$\begin{aligned} \frac{dO}{dt} &= \Psi_0 S(t) - \mu O(t) - \alpha_0 O(t), \\ \frac{dA}{dt} &= \Psi_1 S(t) - \alpha_a A(t) - \mu A(t), \\ \frac{dB}{dt} &= \Psi_2 S(t) - \alpha_b B(t) - \mu B(t), \\ \frac{dC}{dt} &= \Psi_3 S(t) - \alpha_c C(t) - \mu C(t), \\ \frac{dI}{dt} &= \Psi_4 S(t) - \alpha_i C(t) - \mu I(t), \\ \frac{dT}{dt} &= \Psi_5 S(t) - \alpha_t T(t) - \mu T(t), \\ \frac{dX_I}{dt} &= \alpha_0 O(t) + \alpha_a A(t) + \alpha_b B(t) + \alpha_c C(t) + \alpha_g S_H(t) + \alpha_t T(t) + \Psi_6 S(t) - \mu X_I(t) - \rho X_I(t), \\ \frac{dX_C}{dt} &= \rho X_I(t) - \sigma X_C(t) - \mu X_I(t), \end{aligned}$$

$$\begin{aligned}
\frac{dX_H}{dt} &= \alpha_i I(t) - \Omega X_H(t) - \mu X_H(t), \\
\frac{dY_c}{dt} &= \sigma X_c(t) + \Omega X_H(t) - \nu Y_c(t) - \mu Y_c(t)
\end{aligned}
\tag{1}$$

3.6 Reproduction Number (R_0)

The dynamics of the model are highly dependent on the basic reproduction number. The basic reproduction number commonly denoted by R_0 in a given population is the average number of secondary infections caused by a single infectious individual during his/her entire life time as an infective when introduced into a purely susceptible population. The R_0 is directly related to the effort required to eliminate infection. We determine R_0 using the next generation matrix approach [4, 6]. In this approach R_0 is defined as the spectral radius (dominant eigenvalue) of the next generation matrix (operator) FV^{-1} . The matrix operator is formed by distinguishing two disease status, the newly infected and the transfer of the infections into and out of the compartments. This therefore implies that the system of equations corresponding to the infected populations are the ones that are used.

The next generation matrix FV^{-1} is formed from matrices of the partial derivatives of f_i and v_i with respect to the infected classes computed at the disease free equilibrium. The disease free equilibrium is a situation when there is no disease at all in the community. f_i defines the appearance of new infections in compartments i , i being B, C, I, X_I, X_H, X_C and Y_C compartments. It includes only infections that are newly arising but does not include terms which describe the transfer of infectious individuals from one infected compartment to another.

$\mathcal{V}_i = \mathcal{V}_i^{-1} + \mathcal{V}_i^{+}$ where \mathcal{V}_i^{+} is the rate of transfer of individuals into compartment i by all other means other than disease, while \mathcal{V}_i^{-} is the rate of transfer of individuals out of compartment i . From system (1) using the above descriptions

gives

$$\mathcal{F}_i = \begin{bmatrix} \Psi_2 S(t) \\ \Psi_3 S(t) \\ \Psi_4 S(t) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

and

$$\mathcal{V}_i = \begin{bmatrix} \alpha_b B(t) + \mu B(t) \\ (\alpha_c + \mu) C(t) \\ (\alpha_i + \mu) I(t) \\ \alpha_b B - \alpha_c C - \alpha_i I \\ -\rho X_I + \sigma X_c + \mu X_I \\ -\alpha_i I + (\eta + \mu) X_H \\ -\sigma X_c - \eta X_H + (\nu + \mu) Y_c \end{bmatrix}$$

Hence

$$F = \begin{bmatrix} \theta\zeta + \varphi\alpha_b & 0 & 0 & \gamma\rho & 0 & 0 & 0 \\ 0 & \theta + \eta\alpha_c & 0 & \gamma\rho & 0 & 0 & 0 \\ 0 & 0 & \xi + \omega\alpha_i & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

and

$$V = \begin{bmatrix} \alpha_b + \mu & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \alpha_c + \mu & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \alpha_i + \mu & 0 & 0 & 0 & 0 \\ \alpha_b & -\alpha_c & -\alpha_i & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \mu - \rho & \sigma & 0 & 0 \\ 0 & 0 & -\alpha_i & 0 & 0 & k + \mu & 0 \\ 0 & 0 & 0 & 0 & -\sigma & -k & \nu + \mu \end{bmatrix}$$

Where F is the rate at which infected individuals in one compartment produce new infections in the next compartment.

The V^{-1} will be given as

$$V^{-1} = \begin{bmatrix} \frac{1}{\alpha_b + \mu} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{1}{\alpha_c + \mu} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{1}{\alpha_i + \mu} & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\alpha_i}{(\alpha_i + \mu)(\eta + \mu)} & \frac{1}{\eta + \mu} & 0 & 0 & 0 \\ \frac{\alpha_b}{(\alpha_b + \mu)(\sigma + \rho\gamma + \mu)} & \frac{\alpha_i}{(\alpha_c + \mu)(\sigma + \rho\gamma + \mu)} & 0 & 0 & \frac{1}{(\sigma + \rho\gamma + \mu)} & 0 & 0 \\ \frac{\alpha_b \rho\gamma}{(\alpha_b + \mu)(\sigma + \rho\gamma + \mu)(\alpha_c + \mu)} & y_1 & 0 & 0 & \frac{\rho\gamma}{(\sigma + \rho\gamma + \mu)(\sigma_c + \mu)} & \frac{1}{\sigma_c + \mu} & 0 \\ y_2 & y_3 & 0 & 0 & y_4 & \frac{1}{(\alpha_c + \mu)(\nu + \mu)} & \frac{1}{\nu + \mu} \end{bmatrix}$$

where

$$y_1 = \frac{-\alpha_i \rho\gamma}{(\alpha_b + \mu)(\sigma + \rho\gamma + \mu)(\sigma_c + \mu)}$$

$$y_2 = \frac{\alpha_b(\sigma\gamma(\alpha_c + \mu) + \rho\gamma\sigma_c)}{(\alpha_b + \mu)(\sigma + \rho\gamma + \mu)(\sigma_c + \mu)(\nu + \mu)}$$

$$y_3 = \frac{\alpha_c(\sigma\gamma(\alpha_c + \mu) + \rho\gamma\sigma_i)}{(\alpha_c + \mu)(\sigma + \rho\gamma + \mu)(\sigma_c + \mu)(\nu + \mu)}$$

$$y_4 = \frac{\sigma\gamma(\sigma_c + \mu) + \rho\gamma\sigma_c}{(\sigma + \rho\gamma + \mu)(\sigma_c + \mu)(\nu + \mu)}$$

V^{-1} is the average length of time an individual spends in the compartment i during the lifetime. Thus FV^{-1} is

$$\begin{bmatrix} \frac{\theta\zeta + \varphi\alpha_b}{\alpha_b + \mu} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{\theta + \eta\alpha_c}{\alpha_c + \mu} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\xi + \omega\alpha_i}{\alpha_i + \mu} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

FV^{-1} is the expected number of new infections in compartment j produced by an individual in i . The eigenvalues of FV^{-1} are $0, 0, 0, 0, \frac{\theta\zeta + \varphi\alpha_b}{(\alpha_b + \mu)}, \frac{\theta + \eta\alpha_c}{(\alpha_c + \mu)},$ and $\frac{\xi + \omega\alpha_i}{(\alpha_i + \mu)}$

The basic reproduction number (R_0) which is the spectral radius of the matrix FV^{-1} is given by

$$\frac{\theta\zeta + \varphi\alpha_b}{(\alpha_b + \mu)}$$

Increase in R_0 is highly possible in highly endemic areas like Kenya. In these regions Hepatitis B virus mostly spread from mother to child (verical) at birth or through horizontal transmission especially from an infected child to uninfected child during the first 5 years of life and development to chronic infection is very common in these infants. Many infected individuals, both infants and adults are asymptomatic during the initial and chronic stages of the infection

and thus are high risk transmission agents of the virus and of having serious liver disease later. Many chronic infected people progress to cirrhosis and to hepatocellular carcinoma stages.

The parameters in R_0 are particularly those of hepatitis B virus. Increasing θ, ζ and φ increases R_0 and thus the number of those infected with HBV goes up. The next largest eigenvalue is that of HCV

$$\frac{\theta + \eta\alpha_c}{(\alpha_c + \mu)}$$

HIV is also quite significant in the development of HCC in this study with an eigenvalue of

$$\frac{\xi + \omega\alpha_i}{(\alpha_i + \mu)}$$

4 Disease Free Equilibrium

4.1 Local asymptotic stability

The disease free equilibrium points are steady state solutions where there is no disease. The disease free equilibrium (DFE) is locally asymptotically stable and globally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$. The local asymptotic stability of disease free equilibrium (stability that exists for a small t) can be analyzed by calculating the trace and determinant of the Jacobian matrix of the linearized system at disease free equilibrium. The trace and the determinant should be negative and positive respectively while R_0 remains less than one

$$J = \begin{bmatrix} -\mu & -\Psi_2 & \Psi_3 & \Psi_4 & 0 & 0 & 0 & 0 \\ \Psi_2 & -(\alpha_b + \mu) & 0 & 0 & 0 & 0 & 0 & 0 \\ \Psi_3 & 0 & -(\alpha_c + \mu) & 0 & 0 & 0 & 0 & 0 \\ \Psi_4 & 0 & -\alpha_i & -\mu & 0 & 0 & 0 & 0 \\ \Psi_6 + \alpha_g & \alpha_b & \alpha_c & 0 & -\mu - \rho & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \rho & -\delta - \mu & 0 & 0 \\ 0 & 0 & 0 & \alpha_i & 0 & 0 & -\eta - \mu & 0 \\ 0 & 0 & 0 & 0 & 0 & \sigma & \eta & -(\nu + \mu) \end{bmatrix}$$

At disease free equilibrium $B = C = I = X_i = I = X_c = X_H = Y_c = 0$. Thus the Jacobian matrix at disease free equilibrium becomes;

$$J = \begin{bmatrix} -\mu & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -(\alpha_b + \mu) & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -(\alpha_c + \mu) & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\alpha_i & -\mu & 0 & 0 & 0 & 0 & 0 \\ \alpha_g & \alpha_b & \alpha_c & 0 & -(\mu + \rho) & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \rho & -(\delta + \mu) & 0 & 0 & 0 \\ 0 & 0 & 0 & \alpha_i & 0 & 0 & -(\eta + \mu) & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \sigma & \eta & -(\nu + \mu) & 0 \end{bmatrix}$$

The trace at DFE is given by;

$$\begin{aligned} \text{Tr}(E_0) &= -[8\mu + \alpha_b + \alpha_c + \rho + \delta + \eta + \nu] \\ &= -[7\mu + \alpha_c + \rho + \delta + k + \nu + \frac{\theta\zeta + \varphi_b}{R_0}] \end{aligned} \tag{2}$$

which remain negative when $R_0 < 1$.

The determinant at DFE is given by;

$$\text{Det}(E_0) = \mu^2(\alpha_b + \mu)(\alpha_c + \mu)(\mu + \rho)(\delta + \mu)(\eta + \mu)(\nu + \mu) \tag{3}$$

which is positive when $R_0 < 1$. Thus, applying the set conditions then the disease free equilibrium for the system is locally asymptotically stable. It therefore means that when $R_0 < 1$ then there can be no disease for a short time (t).

4.2 Global Asymptotic Stability

The DFE [D^0] of model (1) is globally asymptotically stable (GAS) (stability that exists for a larger t) whenever $R_0 < 1$ and unstable if $R_0 > 1$

Proof. The proof is based on using comparison theorem [13]. The equation of the infected components in the model (1) can be written as

$$\begin{pmatrix} \frac{dB(t)}{dt} \\ \frac{dC(t)}{dt} \\ \frac{dI(t)}{dt} \\ \frac{dX_I(t)}{dt} \\ \frac{dX_C(t)}{dt} \\ \frac{dX_H(t)}{dt} \\ \frac{dX_C(t)}{dt} \end{pmatrix} \leq (F - V) \begin{pmatrix} B(t) \\ C(t) \\ I(t) \\ X_I(t) \\ X_C(t) \\ X_H(t) \\ X_C(t) \end{pmatrix} - \left(1 - \frac{S_H(t)}{N_H(t)}\right) \begin{pmatrix} \theta\zeta + \varphi\alpha_b & 0 & 0 & \gamma\rho & 0 & 0 & 0 \\ 0 & \theta + \eta\alpha_c & 0 & \gamma\rho & 0 & 0 & 0 \\ 0 & 0 & \xi + \omega\alpha_i & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

Since at DFE $S \leq N \forall t \geq 0$ and F and V are as defined in section 2.6.

$$F-V = \begin{pmatrix} \theta\zeta + \varphi\alpha_b - \alpha_b - \mu & 0 & 0 & \gamma\rho & 0 & 0 & 0 \\ 0 & \theta + \eta\alpha_c - \alpha_c - \mu & 0 & \gamma\rho & 0 & 0 & 0 \\ 0 & 0 & \xi + \omega - \mu & 0 & 0 & 0 & 0 \\ -\alpha_b & \alpha_c & \alpha_i & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \mu + \rho & -\sigma & 0 & 0 \\ 0 & 0 & \alpha_i & 0 & 0 & -\eta - \mu & 0 \\ 0 & 0 & 0 & 0 & \delta & \eta & -\nu - \mu \end{pmatrix}$$

Since at DFE $S \leq N \forall t \geq 0$ in ϕ_T then From the fact that not all the eigenvalues of the matrix $F - V$ have negative real parts, it follows that the linearized differential inequality above may not be stable whenever $R_0 < 1$ and as $t \rightarrow \infty$, then $B, C, X_I, X_C, X_H, Y_C \rightarrow (0, 0, 0, 0, 0)$. It is not possible to have DFE for a long time because of the high risk of infection. Even a single infected individual will easily spread the disease especially due to the asymptomatic nature of most infected people. \square

The DFE may not be globally asymptotically stable for $R_0 < 1$ due to the possible backward bifurcation at $R_0 = 1$. For backward bifurcation, there is a sudden abrupt and explosive exchange between Disease Free Equilibrium (DFE) and Endemic Equilibrium. Once $R_0 > 1$ the disease invades to high endemic level.

5 Numerical Simulations

In this section, Matlab software is used to illustrate the numerical simulations describing the theoretical results for Equation (1). The numerical values depend on the particular units chosen. The parameter values are in Table 2.

Table 4: Parameter estimates

Parameter Description	Symbol	Value	Source
Recruitment rate	Λ	2000	Gummel & CIA [5]
Natural death rate		0.4	Assumed
Rate of infection with HBV	μ_H	0.94	variable
Rate of progression to cirrhosis from HBV	μ_V	0.7	Assumed
Rate of contact with HBV infectives	σ_H	0.47	Assumed
Rate of HBV infectives progressing to HCC	θ_H	0.6	variable
Rate of infection with HCV	λ_H	0.49	Assumed
Rate of HIV infected getting to cirrhosis phase	ρ	0.0056	variable
Rate of HCV infected getting to cirrhosis phase	ρ	0.0056	variable
Rate of HCV infected getting to HCC phase	ρ	0.0056	variable

In the absence of infectious risk factor agents; Obesity, Alcohol and the Environment leads to reduced progress to HCC and simulation of the model

results in susceptible individuals being predominant as depicted in Figure 1.

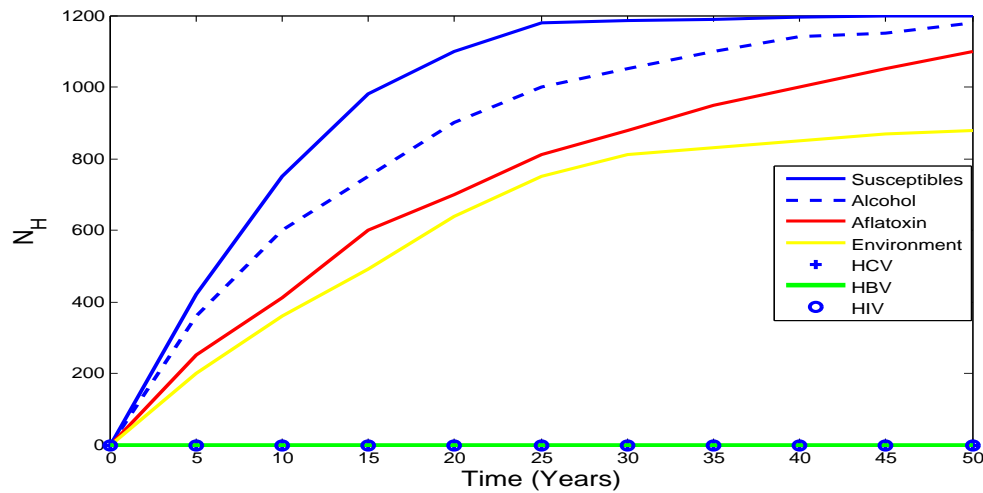


Figure 2: Simulation of disease free equilibrium

The progression to HCC by individuals with HBV infection is quite high and levels off at high rates compared to those of HCV and HIV the non infectious risk are at lower level. If all the individuals are infected at inflammation and cirrhosis stages and no control mechanisms are adhered to, individuals will progress to HCC stage at a faster rate. Figure 2, simulation shows that X_I, X_H, X_C individuals will progress to HCC stage very fast and they become predominant in the population.

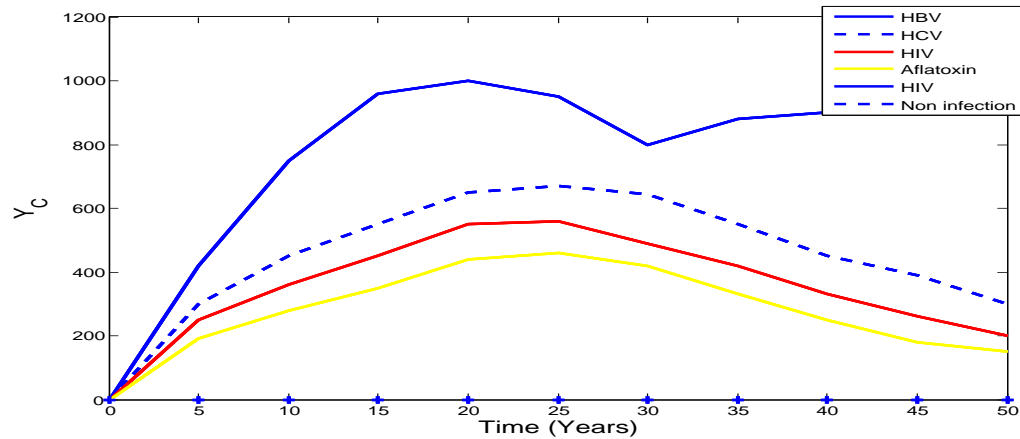


Figure 3: Simulation of disease free equilibrium

6 Discussion

There were more males than females and most of the subjects were young. The patients with HIV had a low mean CD 4+ cell count signifying severe HIV infection and stage. Infectious agents which were associated with HCC included HBV, HCV and HIV infections respectively. This accounted for 56.53% of the risk factors of HCC. Subjects with HCC who did not have known identifiable risk factors were 93 (36.1%), excess alcohol intake in 7 (2.7%), aflatoxins in 2 (0.7%) and genetic predisposition in 5 (2%). Majority of the cases 125 (48.6%) had advanced stage D of HCC [11].

The model depicts that the major risk factors of HCC include viral hepatitis B and C and HIV. The eigenvalues were identified to be higher for HBV followed by HCV and HIV. Most of the subjects with chronic HBV and HCV infections are asymptomatic for long periods making them be sources of infection in the community since they rarely develop acute life threatening diseases. Yet, a significant number of these subjects will develop liver cirrhosis. Indeed, about 85% of chronic HBV infection and 15-30% of chronic HCV infection will lead to liver cirrhosis and HCC within 20 years and approximately 400,000 people in the developing world die of hepatitis C associated liver cirrhosis and HCC

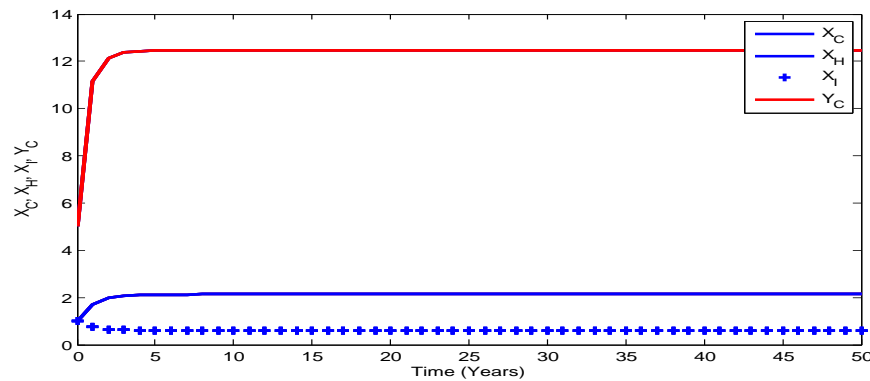


Figure 4: Simulation of use of infected individuals at inflammation stage

annually [18]. However, prevalence of HCV in sub-Saharan Africa is fairly low at 0.5-1.0% and mostly in the Caucasians [15].

Many people infected with hepatitis viruses B and C are not aware because of their asymptomatic status. They continue infecting others and many mothers transmit the infection to their newborn babies by vertical transmission. While there is vaccination against HBV for the infants, there is no public health facility programme for adults who are at risk of HBV infection in Kenya. There is no vaccine for HCV. Treatment coverage for both chronic HBV and HCV infections is low in most high disease burdened settings like Kenya and where available, is provided to patients presenting for care with advanced disease and HCC stage. Chronic HBV and HCV infection is thus a major cause of HCC. People who are chronic carriers of both HBV and HCV have more than a 100-fold increased risk of developing HCC [14]. The progression to HCC increases with age since prevalence is high and treatment is not widely available. In Kenya, many young people between the ages of 20-35 years are diagnosed with HCC as depicted in the study.

HBV/HIV co-infections and HCC in HIV positive patients have been demon-

strated in the Kenyan population [16, 17]. The subjects in this study had severe immunosuppression evidenced by the low CD4+ cell count and are predisposed to HCC. HBV/HIV co-infection may worsen liver inflammation and subsequently fasten the progression to liver cirrhosis and HCC [7, 8, 10]. While HBV and HCV are known risk factors of HCC, HIV has been depicted by this model to be a contributor to development of HCC in Kenya. HIV may worsen and increase the magnitude of HCC in the community and early detection of HCC in HIV positive subjects is vital to prevent liver related mortality.

7 Conclusion

The dynamics of the risk factors of HCC shows that hepatitis B virus is still a major infectious cause of liver cancer. However HIV has been demonstrated to be a risk factor of liver cancer in this population. This shows that without public awareness on the risk factors, individuals with HCC risk factors will easily get liver cancer and will die out faster. Thus, intervention measures need to be instituted to control the risk factors in order to reduce liver cancer in the community.

8 Recommendations

Despite the existence of effective prevention and treatment interventions, HBV and HCV infection continue to be a menace in the society. Due to the fact that acute and chronic HBV and HCV infection is usually asymptomatic few people are diagnosed early enough and they remain asymptomatic until decades after infection when symptoms develop secondary to serious liver damage. Thus there is need to scale up the existing intervention i.e scaling up coverage of infant vaccination, birth dose vaccination, use of peripartum antivirals to hepatitis B antigen positive mothers for prevention of mother to child transmission, and wide testing and treatment of individuals who are already chronically infected with HBV and HCV to prevent viral replication and substantially reduce progress to cirrhosis and HCC.

- (i) There is need for more studies to be done linking HIV and liver cancer in the developing countries.
- (ii) Intervention measures need to be instituted to control the risk factors and this will reduce liver cancer in the community.

- (iii) Improved public awareness will be of necessity to enable the community participate actively in the intervention measures.
- (iv) Policy makers will need to create a supportive system to implement liver cancer prevention and mitigate risk factor spread.

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