eAppendix for "Causal mediation analysis of survival outcome with multiple mediators" by YT Huang and HI Yang

A1. Discussion of Assumptions

The six no unmeasured confounding assumptions would hold if Figure 1 is the true causal DAG. Specifically, the first four assumptions ensure no confounding for causal relationships between S and M_1, between (S, M_1) and M_2, between S and Y, and between (M_1, M_2) and Y (after controlling for $\boldsymbol{X}$); the (5) assumes that there is no alternative path from the baseline HCV viral load S to the baseline HBV viral load M_1 and liver incidence Y through an unknown common mediator, and no path from S to the follow up HBV viral load M_2 and Y through a common mediator other than the baseline HBV viral load M_1; the (6) assumes that there is no alternative path from the baseline HCV viral load S to the baseline HBV viral load M_1 and the follow up HBV viral load M_2 through an unknown common mediator. Additionally, we assume standard assumptions of consistency[1]: counterfactual outcome A_b under the intervention value b equal to the observed outcome A when $B = b$; and positivity: densities of the follow-up HBV DNA M_2 conditional on the baseline HBV DNA M_1, the baseline HCV RNA S and covariates $\boldsymbol{X}$, $[M_2|S, M_1, \boldsymbol{X}]$, M_1 conditional on S and $\boldsymbol{X}$, $[M_1|S, \boldsymbol{X}]$ and S conditional on $\boldsymbol{X}$, $[S|\boldsymbol{X}]$ are greater than 0 with probability 1 for each value of their respective support. Despite the correlation between baseline and follow up HBV DNA, it has been shown that the changes may follow a wide variety of patterns[2], and thus the positivity for the density of $[M_2|S, M_1, \boldsymbol{X}]$ is likely to be satisfied.

We discuss whether the above assumptions are likely to hold for the hepatitis study. We have collected the adjusted for the same set of confounders as existing literatures[3-5] to ensure the causal interpretation for the HBV-liver cancer and HCV-liver cancer relationships (assumptions (1) and (2)). Since the literature has shown that suppression of HBV by HCV occurs within a cell, an organism or an individual[6-10], it is plausible to assume that there is no unmeasured confounding on the HCV-HBV relationship by phenotypic covariates (assumptions (3) and (4)) and that it is unlikely for downstream phenotypic factors affected by HCV to exert undue confounding for the HBV-liver cancer relationship (assumption (5)). It is also plausible to assume that HCV can affect the follow-up HBV viral load only through its baseline viral load (assumption (6)). Taken together, we argue that the above assumptions should be satisfied if confounders for the associations of HBV and HCV with liver cancer are fully adjusted. Note that the effect $\Delta_{S\to M_1 Y}$ consists of two paths: one from S to M_1 and M_2 and then to Y ($\Delta_{S\to M_1\to M_2\to Y}$) and one from S to M_1 and then directly to Y ($\Delta_{S\to M_1\to Y}$). To decompose $\Delta_{S\to M_1 Y}$ to $\Delta_{S\to M_1\to M_2\to Y}$ and $\Delta_{S\to M_1\to Y}$ requires stronger assumptions, which is usually not plausible in application[11,12].

A2. Derivation for the Expression of Counterfactual Outcome

By the six identifying assumptions in main text, one can show that the cumulative distribution function of the counterfactual survival time can be expressed as a double integral with respect to the distributions of the two mediators M_1 and M_2:

$$
\begin{aligned}
&F_{T\left(s_a,M_1(s_c),M_2\left(s_b,M_1(s_c)\right)\right)}(t|\boldsymbol{X}) \\
&= \int\int F_{T(s_a,m_1,m_2)}\left(t|\boldsymbol{X}, M_1(s_c)=m_1, M_2\left(s_b,M_1(s_c)\right)=m_2\right) \\
&\qquad\qquad dF_{M_2(s_b,m_1)}(m_2|\boldsymbol{X}, M_1(s_c)=m_1)dF_{M_1(s_c)}(m_1|\boldsymbol{X}) \\
&= \int\int F_{T(s_a,m_1,m_2)}(t|\boldsymbol{X})dF_{M_2(s_b,m_1)}(m_2|\boldsymbol{X}, M_1(s_c)=m_1)dF_{M_1(s_c)}(m_1|\boldsymbol{X}) && \text{by Assumption (5)} \\
&= \int\int F_{T(s_a,m_1,m_2)}(t|\boldsymbol{X})dF_{M_2(s_b,m_1)}(m_2|\boldsymbol{X})dF_{M_1(s_c)}(m_1|\boldsymbol{X}) && \text{by Assumption (6)} \\
&= \int\int F_{T(s_a,m_1,m_2)}(t|\boldsymbol{X})dF_{M_2(s_b,m_1)}(m_2|\boldsymbol{X})dF_{M_1(s_c)}(m_1|\boldsymbol{X}, s_c) && \text{by Assumption (4)} \\
&= \int\int F_{T(s_a,m_1,m_2)}(t|\boldsymbol{X})dF_{M_2(s_b,m_1)}(m_2|\boldsymbol{X}, s_b, m_1)dF_{M_1(s_c)}(m_1|\boldsymbol{X}, s_c) && \text{by Assumption (3)} \\
&= \int\int F_{T(s_a,m_1,m_2)}(t|\boldsymbol{X}, s_a)dF_{M_2(s_b,m_1)}(m_2|\boldsymbol{X}, s_b, m_1)dF_{M_1(s_c)}(m_1|\boldsymbol{X}, s_c) && \text{by Assumption (2)} \\
&= \int\int F_{T(s_a,m_1,m_2)}(t|\boldsymbol{X}, s_a, m_1, m_2)dF_{M_2(s_b,m_1)}(m_2|\boldsymbol{X}, s_b, m_1)dF_{M_1(s_c)}(m_1|\boldsymbol{X}, s_c) && \text{by Assumption (1)} \\
&= \int\int F_T(t|\boldsymbol{X}, s_a, m_1, m_2)dF_{M_2|M_1}(m_2|\boldsymbol{X}, s_b, m_1)dF_{M_1}(m_1|\boldsymbol{X}, s_c).
\end{aligned}
$$

Note $F_T(t|\cdot)$, $F_{M_2|M_1}(t|\cdot)$ and $F_{M_1}(t|\cdot)$ are cumulative distribution functions of normal variables. With the above result, the average of the transformed counterfactual survival time can also be expressed as a double integral with respect to M_2 and M_1:

$$
\begin{aligned}
&\mathrm{E}\left[H\left(T; s_a, M_1(s_c), M_2\left(s_b, M_1(s_c)\right)\right)|\boldsymbol{X}\right] \\
&= \int H(t)dF_{T\left(s_a,M_1(s_c),M_2\left(s_b,M_1(s_c)\right)\right)}(t|\boldsymbol{X}) \\
&= \int H(t)\int\int dF_T(t|\boldsymbol{X}, s_a, m_1, m_2)dF_{M_2|M_1}(m_2|\boldsymbol{X}, s_b, m_1)dF_{M_1}(m_1|\boldsymbol{X}, s_c) \\
&= \int\int \mathrm{E}[H(T)|s_a, m_1, m_2, \boldsymbol{X}]dF_{M_2|M_1}(m_2|s_b, m_1, \boldsymbol{X})dF_{M_1}(m_1|s_c, \boldsymbol{X}),
\end{aligned}
$$

and so can the probability density function:

$$
\begin{aligned}
&f_{T\left(s_a,M_1(s_c),M_2\left(s_b,M_1(s_c)\right)\right)}(t|\boldsymbol{X}) \\
&= dF_{T\left(s_a,M_1(s_c),M_2\left(s_b,M_1(s_c)\right)\right)}(t|\boldsymbol{X}) \\
&= \int\int dF_T(t|\boldsymbol{X}, s_a, m_1, m_2)dF_{M_2|M_1}(m_2|\boldsymbol{X}, s_b, m_1)dF_{M_1}(m_1|\boldsymbol{X}, s_c) \\
&= \int\int f_T(t|\boldsymbol{X}, s_a, m_1, m_2)dF_{M_2|M_1}(m_2|\boldsymbol{X}, s_b, m_1)dF_{M_1}(m_1|\boldsymbol{X}, s_c).
\end{aligned}
$$

A3. Formulas for Path-specific Effects Using Semiparametric Probit Model

We propose the following three models for the two mediators M_1 and M_2, and the transformed survival time $H(T)$:

$$M_{1i} = \boldsymbol{\delta}_X^T\boldsymbol{X}_i + \delta_S S_i + \epsilon_{M1i}, \text{ where } \epsilon_{M1i} \sim N(0, \sigma_{M1}^2) \quad \text{(A1)}$$

$$M_{2i} = \boldsymbol{\alpha}_X^T\boldsymbol{X}_i + \alpha_S S_i + \alpha_M M_{1i} + \epsilon_{M2i}, \text{ where } \epsilon_{M2i} \sim N(0, \sigma_{M2}^2) \quad \text{(A2)}$$

$$H(T_i) = -(\boldsymbol{\beta}_X^T\boldsymbol{X}_i + \beta_S S_i + \beta_{M1}M_{1i} + \beta_{M2}M_{2i}) + \epsilon_{Ti}, \text{ where } \epsilon_{Ti} \sim N(0,1). \quad \text{(A3)}$$

With the six identifiability assumptions for path-specific effects in the main text, we are able to express the counterfactual outcome as a double integral of the mean of the transformed survival time with respect to the distributions of the two mediators, M_1 and M_2, as shown in Section A1:

$$\begin{aligned}
&\mathrm{E}\left[H\left(T; s_a, M_1(s_c), M_2\left(s_b, M_1(s_c)\right)\right)|\boldsymbol{X}\right] \\
&= \int\int \mathrm{E}[H(T)|s_a, m_1, m_2, \boldsymbol{X}] dF_{M_2|M_1}(m_2|s_b, m_1, \boldsymbol{X}) dF_{M_1}(m_1|s_c, \boldsymbol{X}) \\
&= -[\{\boldsymbol{\beta}_X^T\boldsymbol{X} + \beta_{M1}\boldsymbol{\delta}_X^T\boldsymbol{X} + \beta_{M2}\boldsymbol{\alpha}_X^T\boldsymbol{X} + \beta_{M2}\alpha_M\boldsymbol{\delta}_X^T\boldsymbol{X}\} + \beta_S s_a + \beta_{M2}\alpha_S s_b + (\beta_{M1} + \beta_{M2}\alpha_M)\delta_S s_c].
\end{aligned} \tag{A4}$$

The last expression relies on the independence of S with the errors ϵ_{M1}, ϵ_{M2} and ϵ_T, which would hold under the assumption of no unmeasured confounding.

One can also let the counterfactual outcome as the cumulative distribution function (cdf) of the survival time $F_{T\left(s_a, M_1(s_c), M_2\left(s_b, M_1(s_c)\right)\right)}(t|\boldsymbol{X})$. Again, based on the six identifiability assumptions, we already show in Section A2 that the counterfactual outcome can be expressed as a double integral with respect to M_1 and M_2:

$$\begin{aligned}
&F_{T\left(s_a, M_1(s_c), M_2\left(s_b, M_1(s_c)\right)\right)}(t|\boldsymbol{X}) \\
&= \int\int F_T(t|s_a, m_1, m_2, \boldsymbol{X}) dF_{M_2|M_1}(m_2|s_b, m_1, \boldsymbol{X}) dF_{M_1}(m_1|s_c, \boldsymbol{X}) \\
&= \Phi([\{\log\Lambda(t) + \boldsymbol{\beta}_X^T\boldsymbol{X} + \beta_{M1}\boldsymbol{\delta}_X^T\boldsymbol{X} + \beta_{M2}\boldsymbol{\alpha}_X^T\boldsymbol{X} + \beta_{M2}\alpha_M\boldsymbol{\delta}_X^T\boldsymbol{X}\} + \beta_S s_a + \beta_{M2}\alpha_S s_b \\
&\qquad + (\beta_{M1} + \beta_{M2}\alpha_M)\delta_S s_c]\sigma^{*-1}) \\
&\equiv 1 - \Omega(t|s_a, s_b, s_c),
\end{aligned} \tag{A5}$$

where $\sigma^{*-1} = 1 + \beta_{M2}^2\sigma_{M2}^2 + (\beta_{M1} + \beta_{M2}\alpha_M)^2\sigma_{M1}^2$ and $\Lambda(t)$ is baseline cumulative hazard. Due to the conjugacy property of normal distributions, the second equality shows that the double integral can be further simplified to a function of standard normal cdf that involves the regression parameters for M_1, M_2 and $H(T)$ in (A1)-(A3).

The above expression for $\mathrm{E}\left[H\left(T; s_a, M_1(s_c), M_2\left(s_b, M_1(s_c)\right)\right)|\boldsymbol{X}\right]$ and $F_{T\left(s_a, M_1(s_c), M_2\left(s_b, M_1(s_c)\right)\right)}(t|\boldsymbol{X})$ is based on the models (A2) and (A3) where no S-by-M_1 or S-by-M_2 interaction is assumed. One can easily incorporate these interactions by replacing α_M, β_{M1} and β_{M2} with $\alpha_M + \alpha_{SM}s_b$, $\beta_{M1} + \beta_{SM1}s_a$ and $\beta_{M2} + \beta_{SM2}s_a$, respectively in (A2) and (A3) and thus in (A4) and (A5) because the same development would follow.

With the expressions in (A4) and (A5) and the definition of path-specific effects using counterfactual notations in (1) of the main text, it can be shown that

$$\begin{aligned}
\Delta_{S\to Y}^{Probit} &= \mathrm{E}\left[H\left(T; s_1, M_1(s_0), M_2\left(s_0, M_1(s_0)\right)\right)|\boldsymbol{X}\right] - \mathrm{E}\left[H\left(T; s_0, M_1(s_0), M_2\left(s_0, M_1(s_0)\right)\right)|\boldsymbol{X}\right] \\
&= -\beta_S(s_1 - s_0)
\end{aligned}$$

$$\begin{aligned}\Delta_{S\to M_2\to Y}^{Probit} &= \mathrm{E}\left[H\left(T; s_1, M_1(s_0), M_2\left(s_1, M_1(s_0)\right)\right)|\boldsymbol{X}\right] - \mathrm{E}\left[H\left(T; s_1, M_1(s_0), M_2\left(s_0, M_1(s_0)\right)\right)|\boldsymbol{X}\right] \\ &= -\beta_{M2}\alpha_S(s_1 - s_0) \\ \Delta_{S\to M_1 Y}^{Probit} &= \mathrm{E}\left[H\left(T; s_1, M_1(s_1), M_2\left(s_1, M_1(s_1)\right)\right)|\boldsymbol{X}\right] - \mathrm{E}\left[H\left(T; s_1, M_1(s_0), M_2\left(s_1, M_1(s_0)\right)\right)|\boldsymbol{X}\right] \\ &= -(\beta_{M1} + \beta_{M2}\alpha_M)\delta_S(s_1 - s_0),\end{aligned}$$

$$\begin{aligned}\Omega_{S\to Y_t} &= F_{T\left(s_0, M_1(s_0), M_2(s_0, M_1(s_0))\right)}(t|\boldsymbol{X}) - F_{T\left(s_1, M_1(s_0), M_2(s_0, M_1(s_0))\right)}(t|\boldsymbol{X}) \\ &= \Omega(t|s_a = s_1, s_b = s_0, s_c = s_0) - \Omega(t|s_a = s_0, s_b = s_0, s_c = s_0) \\ \Omega_{S\to M_2\to Y_t} &= F_{T\left(s_1, M_1(s_0), M_2(s_0, M_1(s_0))\right)}(t|\boldsymbol{X}) - F_{T\left(s_1, M_1(s_0), M_2(s_1, M_1(s_0))\right)}(t|\boldsymbol{X}) \\ &= \Omega(t|s_a = s_1, s_b = s_1, s_c = s_0) - \Omega(t|s_a = s_1, s_b = s_0, s_c = s_0) \\ \Omega_{S\to M_1 Y_t} &= F_{T\left(s_1, M_1(s_0), M_2(s_1, M_1(s_0))\right)}(t|\boldsymbol{X}) - F_{T\left(s_1, M_1(s_1), M_2(s_1, M_1(s_1))\right)}(t|\boldsymbol{X}) \\ &= \Omega(t|s_a = s_1, s_b = s_1, s_c = s_1) - \Omega(t|s_a = s_1, s_b = s_1, s_c = s_0).\end{aligned}$$

The point estimates and their variances can be obtained using non-parametric maximum likelihood estimator and functional delta method[13].

A4. Formulas for Path-specific Effects Using Aalen Additive Hazard Model

We propose the same models for the two mediators M_1 and M_2 as (A1) and (A2), and a survival model that hazard is determined linearly by the predictors:

$$\begin{aligned}\lambda_i &= \lambda_0(t) + \boldsymbol{\lambda}_X^T\boldsymbol{X}_i^* + \lambda_S S_i + \lambda_{M1}M_{1i} + \lambda_{M2}M_{2i} \\ &= \Lambda_{Si} + W_{\lambda i},\end{aligned} \tag{A6}$$

where $\Lambda_{Si} = \lambda_0(t) + \boldsymbol{\lambda}_X^T\boldsymbol{X}_i^* + \lambda_S S_i$ and $W_{\lambda i} = \lambda_{M1}M_{1i} + \lambda_{M2}M_{2i}$. M_2 and M_1 are both functions of S and they can take different values of S, .e.g., s_b and s_c. While M_2 and M_1 are determined by s_b and s_c, respectively, it can be shown that $W_{\lambda i}$ is a function of s_b and s_c following a normal distribution G_{W_λ}: $W_{\lambda i}(s_b, s_c) \sim N(\mu_{W_\lambda i}, \sigma_{W_\lambda}^2)$, where $\mu_{W_\lambda i} = \lambda_{M1}(\boldsymbol{\delta}_X^T\boldsymbol{X}_i + \delta_S s_c) + \lambda_{M2}\{\boldsymbol{\alpha}_X^T\boldsymbol{X}_i + \alpha_S s_b + \alpha_M(\boldsymbol{\delta}_X^T\boldsymbol{X}_i + \delta_S s_c)\}$ and $\sigma_{W_\lambda}^2 = \lambda_{M1}^2\sigma_{M1}^2 + \lambda_{M2}^2\sigma_{M2}^2 + \lambda_{M2}^2\alpha_M^2\sigma_{M1}^2 + 2\lambda_{M1}\lambda_{M2}\alpha_M\sigma_{M1}^2$.

With the six identifiability assumptions and the results derived in Section A2, the counterfactual outcome defined as hazard can be expressed as follows:

$$\begin{aligned}&\lambda\left(T\left(s_a, M_1, M_2\left(s_b, M_1(s_c)\right)\right); t\right) \\ &= \frac{\int f_{T\left(s_a, M_1(s_c), M_2\left(s_b, M_1(s_c)\right)\right)}(t)}{1 - \int F_{T\left(s_a, M_1(s_c), M_2\left(s_b, M_1(s_c)\right)\right)}(t)} \\ &= \frac{\int f_T(t|s_a)dG_{W_\lambda}(s_b, s_c)}{1 - \int F_T(t|s_a)dG_{W_\lambda}(s_b, s_c)}\end{aligned}$$

$$
\begin{aligned}
&= \frac{\int \lambda(t|s_a) e^{-\lambda(t|s_a)} dG_{W_\lambda}(s_b, s_c)}{\int e^{-\lambda(t|s_a)} dG_{W_\lambda}(s_b, s_c)} \\
&= \mu_{W_\lambda} + \Lambda_S(s_a) - \sigma^2_{W_\lambda} \\
&= \left\{\lambda_0(t) + \boldsymbol{\lambda}_X^T \boldsymbol{X}^* + \lambda_{M1} \boldsymbol{\delta}_X^T \boldsymbol{X} + \lambda_{M2} \boldsymbol{\alpha}_X^T \boldsymbol{X} + \lambda_{M2} \alpha_M \boldsymbol{\delta}_X^T \boldsymbol{X} - \sigma^2_{W_\lambda}\right\} + \lambda_S s_a + \lambda_{M2} \alpha_S s_b \\
&\qquad + (\lambda_{M1} + \lambda_{M2} \alpha_M) \delta_S s_c.
\end{aligned}
$$

(A7)

The second last equality utilizes the property of moment generating function of normal random variable since W_λ is normally distributed. Similar to the probit model, (A2) and (A6) can be extended to include S-by-M_1 and S-by-M_2 cross-product interaction terms by replacing α_M, λ_{M1} and λ_{M2} with $\alpha_M + \alpha_{SM} s_b$, $\lambda_{M1} + \lambda_{SM1} s_a$ and $\lambda_{M2} + \lambda_{SM2} s_a$, respectively, and so can (A7). By the definition of path-specific effects based on counterfactual notations in (1) of the main text, it follows that

$$
\begin{aligned}
&\Delta^{Aalen}_{S\to Y} = \lambda\left(T\left(s_1, M_1(s_0), M_2\big(s_0, M_1(s_0)\big)\right)|\boldsymbol{X}\right) - \lambda\left(T\left(s_0, M_1(s_0), M_2\big(s_0, M_1(s_0)\big)\right)|\boldsymbol{X}\right) \\
&= \lambda_S(s_1 - s_0) \\
&\Delta^{Aalen}_{S\to G\to Y} = \lambda\left(T\left(s_1, M_1(s_0), M_2\big(s_1, M_1(s_0)\big)\right)|\boldsymbol{X}\right) - \lambda\left(T\left(s_1, M_1(s_0), M_2\big(s_0, M_1(s_0)\big)\right)|\boldsymbol{X}\right) \\
&= \lambda_{M2}\alpha_S(s_1 - s_0) \\
&\Delta^{Aalen}_{S\to MY} = \lambda\left(T\left(s_1, M_1(s_1), M_2\big(s_1, M_1(s_1)\big)\right)|\boldsymbol{X}\right) - \lambda\left(T\left(s_1, M_1(s_0), M_2\big(s_1, M_1(s_0)\big)\right)|\boldsymbol{X}\right) \\
&= (\lambda_{M1} + \lambda_{M2}\alpha_M)\delta_S(s_1 - s_0).
\end{aligned}
$$

The estimation of δ_S and (α_S, α_M) can be carried out with ordinary least square estimator with respective variance/covariance, σ^2_δ and Σ_α, and the estimation of $(\lambda_S, \lambda_{M1}, \lambda_{M2})$ can also be carried out in R library `timereg` with covariance estimate Σ_λ. The variability of the path-specific effects can be approximated by a resampling based method[14,15]. With the point estimates $\widehat{\boldsymbol{\theta}} = \left(\hat{\delta}_S, \hat{\alpha}_S, \hat{\alpha}_M, \hat{\lambda}_S, \hat{\lambda}_{M1}, \hat{\lambda}_{M2}\right)^T$ for $\boldsymbol{\theta} = (\delta_S, \alpha_S, \alpha_M, \lambda_S, \lambda_{M1}, \lambda_{M2})^T$ and their covariance

$$
\hat{\Sigma}_{\boldsymbol{\theta}} = \begin{pmatrix} \sigma^2_\delta & 0 & 0 \\ 0 & \Sigma_\alpha & \mathbf{0} \\ 0 & \mathbf{0} & \Sigma_\lambda \end{pmatrix},
$$

one can sample repeatedly from the multivariate normal distribution with mean $\widehat{\boldsymbol{\theta}}$ and covariance $\hat{\Sigma}_{\boldsymbol{\theta}}$ to obtain a set of realization values $\left\{\widetilde{\boldsymbol{\theta}}^{(1)}, \widetilde{\boldsymbol{\theta}}^{(2)}, \dots, \widetilde{\boldsymbol{\theta}}^{(B)}\right\}$ where B is the number of resampling. Because $\Delta^{Aalen} = (\Delta^{Aalen}_{S\to Y}, \Delta^{Aalen}_{S\to M_2\to Y}, \Delta^{Aalen}_{S\to M_1 Y})$ is a function of $\boldsymbol{\theta}$, the point estimate $\widehat{\boldsymbol{\theta}}$ can be used to calculate the point estimate of Δ^{Aalen}: $\widehat{\Delta}^{Aalen} = \Delta^{Aalen}(\widehat{\boldsymbol{\theta}})$, and by plugging in, $\left\{\widetilde{\boldsymbol{\theta}}^{(1)}, \widetilde{\boldsymbol{\theta}}^{(2)}, \dots, \widetilde{\boldsymbol{\theta}}^{(B)}\right\}$ can be used to calculate the realization of the distribution for $\widehat{\Delta}^{Aalen}$: $\left\{\Delta^{Aalen}\left(\widetilde{\boldsymbol{\theta}}^{(1)}\right), \Delta^{Aalen}\left(\widetilde{\boldsymbol{\theta}}^{(2)}\right), \dots, \Delta^{Aalen}\left(\widetilde{\boldsymbol{\theta}}^{(B)}\right)\right\}$, which can then be used for estimating confidence intervals, e.g., obtain 2.5 and 97.5 percentiles for 95% confidence interval. Covariance of the distribution for $\widehat{\Delta}^{Aalen}$, $\widehat{Cov}(\widehat{\Delta}^{Aalen})$can also be estimated from $\left\{\Delta^{Aalen}\left(\widetilde{\boldsymbol{\theta}}^{(1)}\right), \Delta^{Aalen}\left(\widetilde{\boldsymbol{\theta}}^{(2)}\right), \dots, \Delta^{Aalen}\left(\widetilde{\boldsymbol{\theta}}^{(B)}\right)\right\}$, and thus hypothesis tests can be conducted as $\widehat{\Delta}^{Aalen^T} \widehat{Cov}\left(\widehat{\Delta}^{Aalen}\right)^{-1} \widehat{\Delta}^{Aalen}$.

A5. Formulas for Path-specific Effects Using Cox Proportional Hazard Model

We propose the same models for the two mediators M_1 and M_2 as (A1) and (A2), and a Cox proportional hazard model for the survival outcome:

$$\begin{aligned}\log\lambda_i &= \log\lambda_0(t) + \boldsymbol{\gamma}_X^T\boldsymbol{X}_i^* + \gamma_S S_i + \gamma_{M1}M_{1i} + \gamma_{M2}M_{2i}\\ &= \log\lambda_0(t) + \boldsymbol{\gamma}_X^T\boldsymbol{X}_i^* + \gamma_S S_i + W_{\gamma i},\end{aligned} \tag{A8}$$

where $W_{\gamma i} = \gamma_{M1}M_{1i} + \gamma_{M2}M_{2i}$. Similar to $W_{\lambda i}$, it can be shown that $W_{\gamma i}$ is a function of s_b and s_c following a normal distribution G_{W_γ}: $W_{\gamma i}(s_b, s_c) \sim N(\mu_{W_\gamma i}, \sigma^2_{W_\gamma})$, where $\mu_{W_\gamma i} = \gamma_{M1}(\boldsymbol{\delta}_X^T\boldsymbol{X}_i + \delta_S s_c) + \gamma_{M2}\{\boldsymbol{\alpha}_X^T\boldsymbol{X}_i + \alpha_S s_b + \alpha_M(\boldsymbol{\delta}_X^T\boldsymbol{X}_i + \delta_S s_c)\}$ and $\sigma^2_{W_\gamma} = \gamma^2_{M1}\sigma^2_{M1} + \gamma^2_{M2}\sigma^2_{M2} + \gamma^2_{M2}\alpha^2_M\sigma^2_{M1} + 2\gamma_{M1}\gamma_{M2}\alpha_M\sigma^2_{M1}$.

With the six identifiability assumptions and the results derived in Section A2, the counterfactual outcome defined as log hazard can be expressed as follows:

$$\begin{aligned}&\log\lambda\left(T\left(s_a, M_1(s_c), M_2\left(s_b, M_1(s_c)\right)\right); t\right)\\ &= \log\frac{\int f_{T\left(s_a, M_1(s_c), M_2\left(s_b, M_1(s_c)\right)\right)}(t)}{1 - \int F_{T\left(s_a, M_1(s_c), M_2\left(s_b, M_1(s_c)\right)\right)}(t)}\\ &= \log\frac{\int f_T(t|s_a)dG_{W_\gamma}(s_b, s_c)}{1 - \int F_T(t|s_a)dG_{W_\gamma}(s_b, s_c)}\\ &= \log\frac{\int \lambda(t|s_a)e^{-\lambda(t|s_a)}dG_{W_\gamma}(s_b, s_c)}{\int e^{-\lambda(t|s_a)}dG_{W_\gamma}(s_b, s_c)}\\ &\approx \log\int \lambda(t|s_a)dG_{W_\gamma}(s_b, s_c).\end{aligned}$$

The last equation is an approximation by assuming the outcome is rare and thus $e^{-\lambda(t|s_a)} \approx 1$. It follows that

$$\begin{aligned}&\log\lambda\left(T\left(s_a, M_1(s_c), M_2\left(s_b, M_1(s_c)\right)\right); t\right) \approx \log\int \lambda(t|s_a)dG_{W_\gamma}(s_b, s_c)\\ &= \log\lambda_0(t) + \boldsymbol{\gamma}_X^T\boldsymbol{X}^* + \gamma_S s_a + \mu_{W_\gamma} + \frac{1}{2}\sigma^2_{W_\gamma}\\ &= \left\{\log\lambda_0(t) + \boldsymbol{\gamma}_X^T\boldsymbol{X}^* + \gamma_{M1}\boldsymbol{\delta}_X^T\boldsymbol{X} + \gamma_{M2}\boldsymbol{\alpha}_X^T\boldsymbol{X} + \gamma_{M2}\alpha_M\boldsymbol{\delta}_X^T\boldsymbol{X} + \frac{1}{2}\sigma^2_{W_\gamma}\right\} + \gamma_S s_a + \gamma_{M2}\alpha_S s_b\\ &\qquad + (\gamma_{M1} + \gamma_{M2}\alpha_M)\delta_S s_c.\end{aligned} \tag{A9}$$

Again, (A2), (A8) and (A9) can be extended to include S-by-M_1 and S-by-M_2 cross-product interaction terms by replacing α_M, γ_{M1} and γ_{M2} with $\alpha_M + \alpha_{SM}s_b$, $\gamma_{M1} + \gamma_{SM1}s_a$ and $\gamma_{M2} + \gamma_{SM2}s_a$, respectively.

By the definition of path-specific effects based on counterfactual notations in (1) in the main text, we show the path-specific effects:

$$\Delta_{S\to Y}^{Cox} = \log\lambda\left(T\left(s_1, M_1(s_0), M_2\left(s_0, M_1(s_0)\right)\right)|\boldsymbol{X}\right) - \log\lambda\left(T\left(s_0, M_1(s_0), M_2\left(s_0, M_1(s_0)\right)\right)|\boldsymbol{X}\right)$$
$$\approx \gamma_S(s_1 - s_0)$$
$$\Delta_{S\to M_2\to Y}^{Cox} = \log\lambda\left(T\left(s_1, M_1(s_0), M_2\left(s_1, M_1(s_0)\right)\right)|\boldsymbol{X}\right) - \log\lambda\left(T\left(s_1, M_1(s_0), M_2\left(s_0, M_1(s_0)\right)\right)|\boldsymbol{X}\right)$$
$$\approx \gamma_{M2}\alpha_S(s_1 - s_0)$$
$$\Delta_{S\to M_1 Y}^{Cox} = \log\lambda\left(T\left(s_1, M_1(s_1), M_2\left(s_1, M_1(s_1)\right)\right)|\boldsymbol{X}\right) - \log\lambda\left(T\left(s_1, M_1(s_0), M_2\left(s_1, M_1(s_0)\right)\right)|\boldsymbol{X}\right)$$
$$\approx (\gamma_{M1} + \gamma_{M2}\alpha_M)\delta_S(s_1 - s_0).$$

Again the approximation works well under rare outcome assumption. Estimation and statistical inference (confidence interval calculation and hypothesis testing) are similar to those in Aalen additive hazard model.

A6. Design of Hepatitis Study

The motivating hepatitis study is from a community-based prospective cohort study that was designed to investigate risk factors of liver cancer. The original cohort study recruited 23,820 residents from seven townships of Taiwan from 1991 to 1992, described in previous literature[4,16,17]. Here we focused on 2,888 subjects with available baseline and first follow-up HBV DNA viral load (REVEAL-HBV study). Incident liver cancer (hepatocellular carcinoma) was ascertained by computerized data linkage of the national cancer registry and national death certification profiles in Taiwan from study entry to Dec 31, 2008, and was further verified by medical record. At cohort enrollment, demographic characteristics and other covariates were collected using a structured questionnaire. The serum samples collected at cohort entry were tested for alanine transaminase (ALT) by a serum chemistry autoanalyzer (model 736, Hitachi, Tokyo, Japan), HBV DNA (copies/mL) by the Cobas Amplicor HBV monitor test kit (Roche Diagnostics, Indianapolis, IN) and HCV RNA (IU/mL) by the Cobas TagMan HCV Test v2.0 (Roche Diagnostics). HBV DNA level in serums collected during follow-up examinations was also measured using the Cobas TaqMan HBV Test v2.0 (Roche Diagnostics). 45.2% of the follow-up measurement was within year 1, 27.4% was during year 2-5, 11.4% was during year 6-10, and 16.0% was after 11 years[18]. For the survival analyses, we used the time of measuring the follow-up HBV DNA as the entry time and treated HCV RNA, HBV DNA and covariates measured at study baseline as pre-entry variables. Viral load of HBV and HCV was natural log transformed prior to analyses. Covariates including age with every 10-year increment (30-39, 40-49, 50-59, ≥60 years), gender, ALT levels with three categories (<15, 15-44 and ≥45 IU/L), alcohol consumption (yes/no) and cigarette smoking (yes/no) were adjusted in regression models. Potential nonlinear effects were adjusted by adjusting categorized age and ALT with dummy variables, which was consistent with the previous REVEAL studies[5,19] and made the results comparable.

A7. R Codes for Mediation Analyses Using Cox Proportional Hazard Model and Aalen Additive Hazard Model

R code for the main analyses in Section 4: Data Applications (analysis_aalen_cox_hbvhcvhcc.R)

```
dat<-read.table("dat_hcvhbvhcc_survmed2.txt", h=T)
library(timereg)
library(survival)
source("mediation_aalen_cox_ci_pval.R")
qq<-quantile(dat$logc[dat$logc>0])
dd<-qq["50%"]-qq["25%"]
dat$logc<-dat$logc/dd

method="Aalen"

## 1-mediator

ols_m<-glm(logb2~agegp2+agegp3+agegp4+GENDER+alt1+alt2+smoke1+alcohol1+logc,
data=dat)
aalen_m2<-aalen(Surv(hcc.time/365.25,
hcc.case)~const(agegp2)+const(agegp3)+const(agegp4)+
    const(GENDER)+const(alt1)+const(alt2)+const(smoke1)+const(alcohol1)+
    const(logc)+const(logb2), data=dat, robust=T)
cox_m2<-coxph(Surv(hcc.time/365.25, hcc.case)~agegp2+agegp3+agegp4+GENDER+
    alt1+alt2+smoke1+alcohol1+logc+logb2, data=dat)

if (method=="Aalen"){
    lambdas<-aalen_m2$gamma
    lambdas.var<-aalen_m2$robvar.gamma
} else if(method=="Cox"){
    lambdas<-cox_m2$coef
    lambdas.var<-cox_m2$var
}
mediation_ci1(lambdas[9], lambdas[10], lambdas.var[9,9], lambdas.var[9,10],
lambdas.var[10,10],
   ols_m$coef[10], summary(ols_m)$cov.scaled[10,10], G=10^6, method=method)


## 2-mediator

ols_m1<-glm(logb1~agegp2+agegp3+agegp4+GENDER+alt1+alt2+smoke1+alcohol1+logc,
data=dat)
ols_m2<-
glm(logb2~agegp2+agegp3+agegp4+GENDER+alt1+alt2+smoke1+alcohol1+logc+logb1,
data=dat)
aalen_m3<-aalen(Surv(hcc.time/365.25,
hcc.case)~const(agegp2)+const(agegp3)+const(agegp4)+
    const(GENDER)+const(alt1)+const(alt2)+const(smoke1)+const(alcohol1)+
    const(logc)+const(logb1)+const(logb2), data=dat, robust=T)
cox_m3<-coxph(Surv(hcc.time/365.25, hcc.case)~agegp2+agegp3+agegp4+GENDER+
    alt1+alt2+smoke1+alcohol1+logc+logb1+logb2, data=dat)

if (method=="Aalen"){
    lambdas<-aalen_m3$gamma
    Sigma.lambda<-aalen_m3$robvar.gamma[9:11, 9:11]
} else if (method=="Cox"){
```

```
      lambdas<-cox_m3$coef
      Sigma.lambda<-cox_m3$var[9:11, 9:11]
  }
  alphas<-ols_m2$coef
  Sigma.alpha<-summary(ols_m2)$cov.scaled[10:11, 10:11]
  deltas<-ols_m1$coef
  Sigma.delta<-summary(ols_m1)$cov.scaled[10, 10]

  mediation_ci2(lambdas[9], lambdas[10], lambdas[11], Sigma.lambda,
      alphas[10], alphas[11], Sigma.alpha, deltas[10], Sigma.delta, G=10^6,
  method=method)
```

R code for resampling based method to estimate confidence interval and calculate p-value (see Section A4 in eAppendix) (mediation_aalen_cox_ci_pval.R)

```
## method=="Aalen" -> output Hazard Difference
## method=="Cox"   -> output Hazard Ratio

mediation_ci1 <- function(lambda.s, lambda.g, covar11, covar12,
      covar22, alpha.s, var_alpha, G=10^4, method){
      require(mvtnorm)
      Omega <- matrix(c(covar11,covar12,covar12,covar22),nrow=2)
      IE <- rep(0,G); DE <- rep(0,G); TE <- rep(0,G); Q <- rep(0,G)

      set.seed(137)
      lambda <- rmvnorm(G, mean = c(lambda.s, lambda.g), sigma = Omega)
      alpha <- rnorm(G, mean=alpha.s, sd=sqrt(var_alpha))
      DE <- lambda[,1]
      IE <- lambda[,2] * alpha
      TE <- IE + DE

      DE.obs <- lambda.s
      IE.obs <- lambda.g * alpha.s
      TE.obs <- DE.obs+IE.obs
      pval.DE<-2*min(mean((DE-mean(DE))>DE.obs), mean((DE-mean(DE))<DE.obs))
      pval.IE<-2*min(mean((IE-mean(IE))>IE.obs), mean((IE-mean(IE))<IE.obs))
      pval.TE<-2*min(mean((TE-mean(TE))>TE.obs), mean((TE-mean(TE))<TE.obs))

      if (method=="Cox") {DE=exp(DE); IE=exp(IE); TE=exp(TE)}
      print("DE:")
      print(ifelse(method=="Aalen", DE.obs, exp(DE.obs)))
      print(quantile(DE, c(0.025, 0.975)))
      print(paste("pval_DE=", pval.DE))
      print("IE:")
      print(ifelse(method=="Aalen", IE.obs, exp(IE.obs)))
      print(quantile(IE, c(0.025, 0.975)))
      print(paste("pval_IE=", pval.IE))
      print("TE:")
      print(ifelse(method=="Aalen", TE.obs, exp(TE.obs)))
      print(quantile(TE, c(0.025, 0.975)))
      print(paste("pval_TE=", pval.TE))
}
```

```
mediation_ci2 <- function(lambda.s, lambda.m, lambda.g, Sigma.lambda,
      alpha.s, alpha.m, Sigma.alpha, delta.s, Sigma.delta,
      G=10^4, method){
      require(mvtnorm)
      SY <- rep(0,G); SGY <- rep(0,G); SMY <- rep(0,G); TE <- rep(0,G)
      set.seed(137)
      lambda <- rmvnorm(G, mean = c(lambda.s, lambda.m, lambda.g),
            sigma = Sigma.lambda)
      alpha <- rmvnorm(G, mean = c(alpha.s, alpha.m),
            sigma = Sigma.alpha)
      delta <- rnorm(G, mean=delta.s, sd=sqrt(Sigma.delta))
      SY <- lambda[,1]
      SGY <- lambda[,3] * alpha[,1]
      SMY <- (lambda[,2] + lambda[,3]*alpha[,2])*delta
      TE <- SY+SGY+SMY

      SY.obs <- lambda.s
      SGY.obs <- lambda.g * alpha.s
      SMY.obs <- (lambda.m + lambda.g*alpha.m)*delta.s
      TE.obs <- SY.obs+SGY.obs+SMY.obs
      pval.SY<-2*min(mean((SY-mean(SY))>SY.obs), mean((SY-mean(SY))<SY.obs))
      pval.SGY<-2*min(mean((SGY-mean(SGY))>SGY.obs), mean((SGY-
mean(SGY))<SGY.obs))
      pval.SMY<-2*min(mean((SMY-mean(SMY))>SMY.obs), mean((SMY-
mean(SMY))<SMY.obs))
      pval.TE<-2*min(mean((TE-mean(TE))>TE.obs), mean((TE-mean(TE))<TE.obs))

      if (method=="Cox") {SY=exp(SY); SGY=exp(SGY); SMY=exp(SMY); TE=exp(TE)}
      print("SY:")
      print(ifelse(method=="Aalen", SY.obs, exp(SY.obs)))
      print(quantile(SY, c(0.025, 0.975)))
      print(paste("pval_SY=", pval.SY))
      print("SGY:")
      print(ifelse(method=="Aalen", SGY.obs, exp(SGY.obs)))
      print(quantile(SGY, c(0.025, 0.975)))
      print(paste("pval_SGY=", pval.SGY))
      print("SMY:")
      print(ifelse(method=="Aalen", SMY.obs, exp(SMY.obs)))
      print(quantile(SMY, c(0.025, 0.975)))
      print(paste("pval_SMY=", pval.SMY))
      print("TE:")
      print(ifelse(method=="Aalen", TE.obs, exp(TE.obs)))
      print(quantile(TE, c(0.025, 0.975)))
      print(paste("pval_TE=", pval.TE))
}
```

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